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ORIGINAL ARTICLES.

THE RENAL LESION IN BRIGHT'S DISEASE.*

By T. Addis, M.D.,

SAN FRANCISCO, CALIF.

(From the Department of Medicine, Stanford University Medical School.)

A TITLE such as "The Renal Lesion in Bright's Disease" suggests a dissertation on the structural defects found in the kidney after death. But I want to talk about the changes which occur in the kidney during life, or, rather, I want to talk about a way by which we may possibly learn to follow the changing fortunes of the renal lesion, to understand something about its nature and extent, to recognize alterations in its intensity and localization, so that we may begin to be able to piece together the whole story of the course and development of the renal lesion during the life-time of the patient. This of course will not be the story of Bright's disease, for Bright's disease is much more than a renal lesion and contains a multiplicity of problems which for the most part we cannot even clearly formulate. But when attention is narrowed on such a fragmentary aspect of the disease as the renal lesion we soon come to certain clear questions which may not be unanswerable.

Before our special subject can be dealt with we must answer the primary question as to what is meant by the term Bright's disease. From the nature of our problem the definition must be given in clinical, not in anatomic terms, and on that account we must be content with something less exact and more inclusive than the answer which might satisfy a morphologist. This group of patients was first distinguished by the discovery that their urine contained a

* Read before the Harvey Society, April 27, 1928.

heat-coagulable protein and this is still the initial step in clinical diagnosis. The next step followed when the microscope became a clinical instrument, and it was found that the urine of many patients with protein in their urine contained cylindrical bodies which came to be called casts, because they were molds of the interior of the renal tubules. These structures which the clinician saw in the urine during life the pathologist also saw filling the lumen of some of the tubules after death. It will be noted that when the presence of casts as well as of protein in the urine was required several diverse groups of patients were excluded from the diagnosis of Bright's disease. Infections of the renal tissue by pyogenic organisms and by the tubercle bacillus, or the invasion of renal tissue by new growth, may be associated with the presence of some protein in the urine, but since such processes tend toward the complete destruction of the renal elements, they remove the very conditions on which cast formation depend. Cast formation must be a result of pathologic processes which may distort but do not entirely obliterate the normal renal architecture and function, for without *some* sort of tubule and *some* flow of urine no casts can be formed. Last with the development of methods for the separate collection of urine from each kidney came the independant clinical recognition of the fact that the conditions grouped under the heading—Bright's disease—always affect both kidneys at once, a fact which of course had already long been established by the pathologists.

I do not feel that from the purely clinical standpoint we can as yet say more than that Bright's disease is any condition in which more than the normal amount of protein and more than the normal number of casts are to be found in the urine coming from both kidneys. It is true that this seems a poverty-stricken definition in contrast with the wealth of the symptomatology often seen in these patients, but it has the great virtue of resting only on two invariable and readily ascertainable clinical phenomena. It is of course open to the objection that it dignifies with the name of Bright's disease all the transient albuminurias and cylindurias which are associated with many forms of toxemia and of bacterial infection. But who can say that a study of just such conditions may not give a clue to the understanding of the more lasting renal lesions which are usually classified as Bright's disease? For the present, definitions which may include too much are to be preferred to those which tend to narrow the field of investigation by the requirement of signs which may not be invariably present or present only in certain stages of the disease. Edema and renal functional abnormalities come and go, and cardiac enlargement and arteriosclerosis may never develop, but so long as we can detect abnormalities in the rate of protein and cast excretion we have direct evidence of a certain type of renal lesion and may say that the patient has some form of Bright's disease.

But the very breadth of this definition makes it all the more necessary that its limits be clearly drawn. If we are interested in Bright's disease only insofar as it constitutes an immediate and serious menace to health, we can perhaps afford to be content with the heat and acetic acid test for protein in the urine and with a laboratory technician's report as to the presence or absence of casts in the urinary sediment. But our long dependence on such methods has made us accustomed to the erroneous supposition that there are only two classes of urine, those which contain protein and casts and those which do not. In reality all urines contain protein and in all urinary sediments casts may be found. Our definition therefore has no meaning until it is expressed in quantitative terms. There is no qualitative difference between the urine of normal individuals and the urine of patients with Bright's disease, the difference is solely one of *quantity*. It is not the presence of protein and casts in the urine, but the finding of more protein and of a greater number of casts than are usually present which brings any individual within the scope of our definition.

This situation necessitates the development of methods which may enable us to measure the extent of variation in the rate of excretion of protein and casts in the urine of people whom we take to be "normal." In a crude and preliminary manner this has been done. The determination of the small amount of protein in the urine of normal individuals by such standard methods as Kjeldahl determinations is a difficult and laborious procedure, and the estimation of protein in urine by the various clinical methods was shown by Messrs. Shevky and Stafford[1] to be extremely inaccurate and quite inapplicable for the estimation of very low protein concentrations. But they observed that an acid alcoholic solution of phosphotungstic acid such as is used in Tsuchiya's modification of Esbach's method, gave after centrifuging a bulky precipitate, even from solutions containing small concentrations of protein. By comparing the volume of precipitate obtained under fixed conditions with the concentration of protein as determined by the Kjeldahl method they were able to develop a method whereby it was possible to obtain a rough measure even of rates of protein excretion which were so low that they approached the limits of the normal. We have been able to improve on this method in some details and hope that ultimately we shall be able to measure the variations in the rate of protein excretion in normal individuals. In the meantime through observations on many normal individuals and on many patients who were passing from what we call Bright's disease back to "normality" we have reached the tentative conclusion that the upper limit of normal variation is in the neighborhood of 30 mg. of protein per twelve-hour period.

The principal difficulty in the way of measuring the rate of cast excretion lies in the wide fluctuations in the composition of the urine.

It happens that there are certain combinations of physical properties frequently met with in urine which are directly destructive of the elements we want to measure. For instance all the casts in urine, with the exception of epithelial casts and their derivatives, are composed of a substance which dissolves as the hydrogen-ion concentration and the salt concentration of the urine falls. These casts are therefore never found in dilute and alkaline urines. Advantage may be taken of this property of hyaline casts to separate the substance of which they are composed from the other formed and unformed urinary constituents. The sediment obtained by centrifuging urine contains a mixture of all sorts of cells and casts. If the urine is drawn off and replaced by 0.9 per cent NaCl solution the hyaline casts are still preserved. The addition of a slight excess of NH_4OH will dissolve them and now on certrifuging the supernatant salt solution contains the hyaline cast material. The addition of a certain amount of acetic acid precipitates the material in an amorphous gelatinous form which may be centrifuged off, redissolved in salt solution made alkaline with NH_4OH and reprecipitated as often as is necessary to effect a practically complete separation from the urine. The material when dry contains about 12 per cent of nitrogen. Its general reactions are those of a protein but it differs from the other proteins of the urine not only in regard to its solubility in NH_4OH and its precipitation by weak acids, but also in the fact that a considerable amount of a reducing substance is formed when it is heated with acids. These properties make it seem likely that the substance of which hyaline casts are formed is a compound of a protein and chondroitin sulphuric acid. Since chondroitin sulphuric acid combines with many proteins, including serum albumen and serum globulin, it is probable that its composition is not constant. But doubtless the conditions required for the precipitation in the test tube are those which are required for precipitation within the lumen of the renal tubules and the chondroitin sulphuric acid which is a constituent of all urine will precipitate protein in the form of a gelatinous mold of the tubule whenever a sufficient hydrogen-ion and salt concentration is attained. But these conditions are by no means always fulfilled, and so it happens that in the urine of the same individual hyaline casts come and go from day to day or even from hour to hour. To a lesser degree this same inconstancy characterizes the presence in the urine of the other division of casts, the epithelial casts and its granular and waxy varieties, for the formation of these cellular molds appears to be prevented whenever there is more than a certain rate of flow of fluid down the tubules. Finally there is another formed element, the red blood cell, whose rate of excretion under ordinary conditions varies widely simply because the salt concentration of the urine is sometimes so low that even the stromata of the lysed cells become invisable.

These are the difficulties which have made it seem absurd to use

quantitative methods in studying the urinary sediment. But once their nature is recognized it is not difficult to circumvent them. There are in reality only two essential conditions, a sufficient molecular concentration and a sufficient degree of acidity. The minimum of each varies with the other, so that for instance, a relatively dilute urine will fulfill the requirements if the hydrogen-ion concentration is high, while a considerably greater concentration is necessary if the urine is neutral. No fixed limit can be set for either alone. But if a patient abstains from fluid during the day and collects the night urine the conditions are nearly always fulfilled. There is one important exception. In patients in whom the amount of functioning renal tissue has been reduced to less than half the normal amount the blood-urea concentration begins to rise and when the kidney is reduced to a quarter or less of its original size there is such a considerable increase in the blood-urea concentration that this factor alone is sufficient to prevent the remnant from excreting any but a dilute urine.[2] In practically all other patients with Bright's disease, however, this simple regulation is sufficient. There is only one other point. The collection must be exactly timed in order that the results may be expressed not as concentrations but as rates of excretion of casts, red blood cells, white blood cells, and epithelial cells and protein per unit of time.[3]

Counts made under these conditions on 74 apparently healthy medical students showed an average excretion of 1040 casts per twelve hours with a range of from 0 to 4270. The average rate of red blood-cell excretion was 65,750 per twelve hours, varying from 0 to 425,000. The white blood cells and epithelial cells were excreted at an average rate of 322, 550 per twelve hours and the range was from 32,400 to about 1,000,000.[4]

We now have a first approximation toward a definition of Bright's disease. We may say that it includes all individuals who excrete more than 30 mg. of protein per twelve hours and in whose urine, under the conditions specified, more than 5000 casts per twelve hours are eliminated.

We begin then with a clinically observed abnormality. But what lies behind? Can it be the result of a functional rather than of a structural disorder of the kidney? If we could see the renal cells might they seem whole and perfect, although somehow or other they were failing in their appointed task of keeping the protein molecules of the plasma from slipping past them into the urine? Or for that matter might we find not only that the architecture of the kidney was intact but that all its cells were working together in true unison, so that we should have to look for the lesion quite beyond the kidney, perhaps at the site of formation of an imperfect protein or where the precursors of the materials of cast formation are elaborated? Of course if either of these hypotheses were true it would be well to postpone all other explorations until we had uncovered *some*

anatomic defect, for it is through the gate of structural pathology that we enter on the direct road to a knowledge of disease. It is when we handle the disorganized tissue, when we see the distorted cells, or by the aid of weights and measures discover the disorientation of molecular structure that we make one step which we surely need never retrace on the long way toward any real understanding of a disease entity. This first step was taken by Richard Bright more than a century ago, when he observed the constant association between proteinuria and bilateral nonsuppurative renal lesions. You will remember that even his title page expresses his sense of the importance of the relation between clinical and structural abnormalities, for he described his work as "illustrating the symptoms and cure of disease *by a reference to morbid anatomy.*"[5] But since the time of Bartels[6] we have wandered from this royal road and have lost ourselves in a maze of speculation in regard to renal function. It was only the other day that Volhard and Fahr[7] found the way back to the place where Bright and Bartels had been forced to stop, and it is along the road which they have again begun to open up that for a time at least we may most hopefully travel. So, without rejecting the other hypotheses I have mentioned as necessarily entirely erroneous, let us start with the one which we know represents at least part of the truth, the one which relates the proteinuria and cylinduria to a renal lesion. Here we stand on firm ground and on our own feet, even apart from all the combined clinical and pathologic testimony of the past, for in the urine of patients with what has just been defined as Bright's disease we find direct evidence of the existence of a renal lesion.

Given then a patient with Bright's disease there are two questions which immediately present themselves. First, what is the *extent*, and second what is the *nature* of the renal lesion? These are old questions and all clinical observation and all tests of renal function have tried to answer them. But I submit that the answers given have been indefinite and of diminished practical value not because there was any lack of acuity in the clinical observation or any failure of ingenuity in the tests of function, but solely because these questions are quantitative questions while the methods which have been used are qualitative methods which can return only qualitative answers.

It is obvious that when you ask what is the extent of a renal lesion you are asking *how much* of a lesion there is and that nothing but a quantitative answer will suffice. It is not enough to answer that there is a tendency toward "a fixation of the specific gravity of the urine" or even to say that there is a rise in the nonprotein nitrogen of the blood or a phenolsulphonephthalein excretion which is less than normal. These answers are better than nothing but they are qualitative answers even though given in numerical terms, and do not satisfy the precision which the question demands. We can

answer that question only by devising a quantitative method. But how can the extent of a renal lesion be measured in a living man? We know by a glance at the small scarred remnants of kidneys which we see at the postmortem examination of some of our patients that renal lesions sometimes decrease the amount of functioning renal tissue. But in the living patient we can only measure what the kidneys do. Yet if there are conditions under which a fixed relation exists between the amount of renal tissue and some quantitative measure of renal function, we might through function attain to a measurement of the amount of renal tissue. Then in any of our patients we might by successive measurements say now he has 90 per cent, now 70 per cent, now 30 per cent, and now only 10 per cent of the usual amount of functioning renal tissue, and in that sense we should have arrived at a clinical answer to the question as to the extent of the renal lesion.

Part of the function of the kidney consists in moving urea from the blood into the urine. Now, regardless of the mechanism by which this is accomplished, we may conceive the blood passing through the kidney as consisting of two portions, a portion which passes through unchanged and another portion from which the urea is completely removed. The volume of this urea-free part of the blood can be determined, for if the whole blood is found to contain B mg. of urea per unit volume, and the urine is found to contain D mg. of urea per unit of time, the volume of blood completely freed from urea per unit of time is $\frac{D}{B}$, which is the ratio between the rate of urea excretion and the blood-urea concentration.* Considered in this light such a ratio should be a quantitative measure of kidney function and under proper conditions might measure the amount of functioning renal tissue.

But are there any conditions under which this urea ratio is determined only by the amount of renal tissue? If the kidneys were simply filters of uniform texture but varying size, and they were all filled to the top with water, we might determine the relative size of the filters from the rates of filtration. But though for certain purposes it may be advantageous to regard the kidney as a special sort of filter, a little experience with its apparently irregular and bizarre filtering is enough to convince anyone that it must have all sorts of peculiarities about which we know very little. A group of workers at Stanford University Medical School have spent a good deal of time during the past fifteen years in trying to understand how it comes about that the same renal filter filled presumably with the

* I am indebted to my colleague, Professor G. D. Barnett, for this conception of the meaning of the ratio. He pointed out, soon after the publication of the paper on the ratio as a method for determining the amount of renal tissue,[12] that it was only through recognizing that the ratio was the volume of blood freed from urea that it could be thought of as a concrete and reasonable measure of function.

same amount of fluid can deliver such varying quantities of filtrate.[8] Undoubtedly one of the most interesting observations of this sort was the discovery that the amount of blood freed from urea per unit of time was increased by the addition of minute amounts of adrenalin, decreased by equally minute quantities of pituitrin, and left unaffected when the same doses of adrenalin and pituitrin were added together.[9] But for our present purposes all these interesting and possibly even important observations are only indications of conditions which we must eliminate or neutralize if we are to attain to that constant relation which we desire.

In 1916 Dr. Watanabe and I[10] found that our urea ratio was not under all conditions a measure of the amount of renal tissue, for we were able to reduce the amount of renal tissue to half its original quantity by ligation of one ureter without producing any marked effect on the magnitude of the urea ratio. It was only when we put the kidneys under strain by administering considerable amounts of urea and water that the lowered urea-ratio values revealed the loss of renal tissue. The recent work of Richards and Schmidt[11] enables us by analogy to construct an hypothesis as to why full renal activity is a necessary condition before urea-ratio values can be translated into terms of renal tissue. Their anatomic observations on amphibian kidneys suggest that in mammals also the renal elements under ordinary conditions are not all functioning at the same time, and that just as they saw the blood begin to flow again through the empty glomeruli of their frog's kidneys when urea was injected into the circulation, so in man also the renal elements may be wakened to activity when we give urea and water. At least we may thus account for the increase in the value of the urea ratio and for its greater constancy in both man[12] and the rabbit[13] after the administration of urea and water.

The real problem is the definition of the conditions under which the urea ratio varies directly as the amount of renal tissue. In man these conditions are approached when no food is taken and hourly rates of urea excretion with corresponding blood-urea concentration determinations are measured during the fourth, fifth, and sixth hours after urea has been taken and while an active diuresis is being maintained by water drinking.[14] In rabbits the ideal conditions cannot be so nearly approached but here we have the advantage that we can measure the amount of renal tissue at the end of an experiment and find how closely we have been able to predict the observed value from the urea ratio results. This has been done in several ways[15] with a reasonably satisfactory agreement between fact and theory. The most direct method was the plotting of the urea-ratio values against the weight of the kidneys of very small to very large rabbits and the curve indicated a direct proportion between urea-ratio value and renal weight.[16] Finally, if under our chosen conditions the urea ratio really measures the amount of renal tissue, then in the

same individual since the amount of renal tissue is constant, the urea ratio should also be constant. Dr. Drury and I[17] found that a series of single ratios carried out on ourselves had coefficients of variability (the standard deviation expressed as a percentage of the mean) of 5 per cent and 6 per cent, respectively, and Mr. Scott Polland has just completed a series on himself which has a coefficient of variability of only 4 per cent.[18]

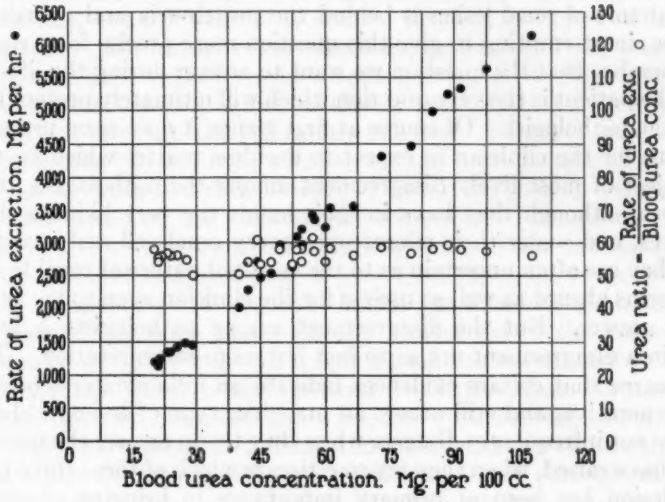


FIG. 1.

A series of urea-ratio determinations on the same individual under the required conditions but at varying blood-urea concentrations is shown in Fig. 1. The graph shows that provided the necessary conditions are complied with the urea ratio is independent of the level of blood-urea concentration or of the rate of urea excretion. No matter whether the blood-urea concentration is 20 or 100 mg. per 100 cc. or the rate of urea excretion 1000 or 5000 mg. per hour, the ratio value remains about 56 (that is 56 times 100 cc. of blood washed free from urea). Now Dr. Drury[19] has shown that this remains approximately true far beyond these limits. He injected relatively enormous quantities of urea into the blood stream of rabbits and even at blood-urea concentrations of over 750 mg. per 100 cc. the kidney increased the output of urea proportionately so that even then the same volume of blood was still washed free from urea. This seems to indicate that under these conditions the kidney passively responds to an increase in blood-urea concentration just as a filter would. This, however, is merely a speculation and does not alter the empirically observed fact that there are attainable conditions under which the determination of the volume of blood washed

free from urea is an approximate measure of the mass of renal tissue. It is this fact which gives us confidence that successive ratio measurements on our patients* do truly indicate the changes which occur in the amount of still functioning renal tissue, and thus allow us to determine the extent of a renal lesion and to follow the changes in the extent of the lesion throughout the course of its development.

There remains the second question, the question as to the nature of the renal lesion. Is there any way by which we may hope to find what sort of renal lesion is behind the proteinuria and cylinduria? Now, in attempting to give this question more precise form we can remember that the question we want to answer during the life-time of the patient is the very question which will ultimately present itself to the pathologist. Of course at first glance it does seem presumptuous for the clinician to expect to decide a matter which is still a subject of most lively disagreement among the pathologists themselves, although they have in their hands the very kidneys themselves, and under their microscopes every renal cell and structure. If they are often uncertain as to the essential nature of renal lesions, it seems absurd as well as useless for the clinician even to try to find the answer. But the disagreement among pathologists is in the main a disagreement not as to fact but as to interpretation. They all agree that certain evidences indicate an inflammatory, others a degenerative, and still others an atrophic, type of lesion, although they not infrequently disagree when they try to answer the question we have raised, when they try to estimate which of these three types of lesion has been of primary importance in bringing about the complex of lesions which is finally found in every case of Bright's disease. For when a pathologist asks himself what is the "nature" of a renal lesion he means what was the original morphologic abnormality which may have initiated the series of changes which ultimately produced the scarred, degenerated, and atrophied kidneys he has before him. Was it some long past glomerular inflammation with subsequent degeneration and atrophy? Or was the arteriolar thickening that he observes the really essential lesion, which slowly led to secondary inflammatory reactions, to degenerative changes and to a gradual replacement of glomeruli by fibrous tissue? These are not easy questions for the pathologist to answer because his observa-

* Quite apart from disease, the kidneys of small individuals are in general smaller than those of large individuals. We found that in rabbits the most direct relation between kidney weight and body size was obtained when the body surface was used as the measure of size.[16] Dr. L. L. MacKay and Dr. E. M. MacKay[20] have recently published results of a very complete and extensive investigation of the relation of the kidney weight of normal rats to various measures of body size. They have shown quite conclusively that the kidney weight per unit of body surface is approximately the same for all sizes of rats, whereas the kidney weight per unit of body weight or body height varies with size. On this account the average ratio obtained on normal human male adults[14] has been expressed in relation to body surface as 2770 cc. of blood freed from urea per hour per square meter of body surface. The ratios obtained on patients are given as percentages of this average normal value.

tion is restricted to a single last cross section of a process which has been developing for years or for decades. He must in imagination rebuild the whole evolution of the lesion. And just as the clinician has often, not unwisely, declined to attempt what seems beyond him, so also the pathologist may in the end grow weary of speculation and may refuse to try to give an answer. Both groups have their own difficulties. The pathologist sees only the end and must try to reconstruct the beginning. The clinician sees the beginning as well as the end, but for want of a method he does not know what is happening. His history of extrarenal symptoms, his blood pressure records, his observations on the specific gravity of the urine and the percentage of phenolsulphonephthalein excretion are sometimes helpful but they are not sufficiently specific. After all, a morphologic question can be finally satisfied only by a morphologic answer.

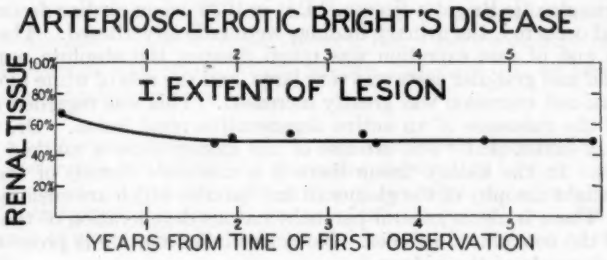
What we want is a clinical method which will give us an insight into the nature of the predominant morphologic changes as they occur in the kidney from the very beginning of the process from month to month and from year to year throughout the whole course of the development of the renal lesion. It does not seem to me unreasonable to hope that with the attainment of the necessary constancy of the urine by the simple means I have outlined we may gradually learn through trial and error to construct from our rates of protein, cast, red blood-cell and white and epithelial-cell excretion a knowledge as to whether inflammation, degeneration or atrophy of renal tissue is the original and continuing lesion throughout the evolution of the process or whether, as some pathologists are inclined to believe, the evidence at postmortem examination for the predominance of one or other of these three types of lesion is a more or less accidental circumstance, depending perhaps on the varying intensity of action of the same toxin, or on the changing susceptibility, now of the glomeruli, now of the tubules, and now of the vessels to one and the same injurious agent. One has only to recall the picture of a glomerulus in active inflammation, with Bowman's capsule filled with red blood cells and leukocytes, to feel that the sediment from the urine of such a kidney should have a characteristic morphology, quite distinct from that of urine from a kidney in which arterial disease is the cause of a slow process of atrophy or from that of urine from a kidney in which the lumen of the tubules is filled with desquamated renal cells and the tubule epithelium the seat of cloudy swelling and fatty degeneration. But such *a priori* considerations are only of value as an incentive to the making of observations. The only way seems to be the laborious one of repeatedly determining in every patient with Bright's disease the extent of the renal lesion and the rates of excretion of the various formed elements of the urine, quite irrespective of the frequently obvious clinical uselessness of such elaborate procedures, in the hope that as time passes there shall come at least in some of these cases

the opportunity to interpret the meaning of the clinical record in the light of the structural abnormalities revealed at postmortem and so to learn to translate the clinical data into anatomic terms that we may in the end attain to a knowledge of the structural evolution of the renal lesion.

I do not need to tell you that this ambitious program has not yet been carried out. It has in fact been only very sketchily begun. It has been approached in an entirely empirical fashion in that measurements made on all sorts and varieties of patients with Bright's disease were arranged in groups without taking any account of ideas derived from the history or physical examination. The classification is identical with the one I gave some years ago when average rates of protein, cast and cell excretion from living patients were presented.[3] It was observed that some patients always have an abnormal rate of red blood-cell excretion, so they are said to have hemorrhagic Bright's disease. There is another group with a normal number of red blood cells but with a high rate of excretion of casts of the epithelial type and of epithelial cells in various stages of degeneration. This is the group with degenerative Bright's disease. And then there is a third group in whose urine there is no marked abnormality in red blood-cell or epithelial-cell excretion but who manifest a relatively slight excess of protein and cast excretion over long periods of time. For want of a better name this last group is called arteriosclerotic Bright's disease on the supposition that such slight abnormalities arise from a slow atrophy of renal tissue due to arteriosclerosis of the renal vessels. I recognize of course the gross lack of formal unity involved in the conjunction of two directly descriptive terms such as hemorrhagic and degenerative with a third, which is neither descriptive nor direct. But it is a convenient word and the violation of internal harmony makes it apparent that this so-called classification is only a temporary device, a local scaffolding which will disappear as the whole structure of our knowledge of Bright's disease is gradually built. As the years have gone by some of our patients have died and the knowledge derived from a comparison of the urinary findings with the structure of the kidney itself has caused, and still causes, a slow shifting of the criteria on which the classification is made and has led to many changes in the ideas originally entertained in regard to the meaning of the observed urinary abnormalities. But the main outlines seem now to be securely fixed. Dr. Jean Oliver of the pathological department of Stanford University Medical School is working with me on a study of the 75 patients on whom renal observations were made after death as well as during life. A critical judgment must wait for this report. At present I can only cite a few cases.

I shall give first an instance of what I have called arteriosclerotic Bright's disease. (Fig. 2.)

The patient was an old man who died this year of bronchopneumonia. I met him first sixteen years ago. At that time he had hypertension and a small amount of protein and a few hyaline casts in his urine. The hypertension slowly disappeared but the evidences of a renal abnormality remained. The extent of the renal lesion (shown in the upper part of Fig. 2) is considerable. In 1920, only 67 per cent of the average normal amount of renal tissue remained and in 1922 there was a further decrease to about 50 per cent but thereafter this value was constantly maintained. Here then is a lesion which has destroyed half of the kidney and yet one in which the rate of progression is so slow that over a period of years we are unable to detect any significant advance. The evidence as to the nature of this lesion is given in the lower part of Fig. 2. The rate of protein excretion was only once above the upper limit of normal. The number of casts never exceeded three times the normal upper limit. They were almost all hyaline casts without fat droplets. The absolute number of epithelial and granular casts was always low. The rate of excretion of red blood cells was never certainly abnormal and the number of white blood cells and of epithelial



NATURE OF LESION.

Date.	Protein, mg. per 12 hours.	Cast excretion, No. per 12 hours.	Red blood cells, No. per 12 hours.	White and epithelium cells, No. per 12 hours.
March 12, 1924	20	8,200	945,000	580,000
March 31, 1925	20	17,100	830,000	308,000
May 18, 1926	—	4,500	0	162,000
April 4, 1927	82	3,200	105,000	23,000

FIG. 2.

cells do not allow us to suppose that there was any excessive desquamation of renal cells. The lesion then was relatively inactive in spite of the considerable destruction of renal tissue. And yet it was still in process of evolution for always over sixteen years there was some evidence of its action. That we were observing the effects of a slow destruction of localized areas of the kidney due to arteriosclerosis of the renal vessels was an obvious inference.

Dr. Oliver's summary of his findings is as follows:

"The kidneys are slightly smaller than normal, measuring 10 by 5 by 3 and 9 by 5 by 2.5 cm., respectively. The capsule strips easily leaving a fine granular red surface. The cut surface shows some narrowing of the cortex. The renal arteries are distinctly thickened. Sections show many fibrous scars in the cortex with atrophy of the tubules and fibrosis of the glomeruli. There are no inflammatory lesions in the latter, nor significant degenerative changes in the former. The arteries show an extreme fibrous thickening of their intima, especially marked in the small branches which extend into the cortex."

In patients with renal arteriosclerosis a cerebral accident or cardiac decompensation is occasionally followed by a superimposed degenerative process which hides the underlying original arteriosclerotic lesion.

Date.	Protein, mgs. per 12 hours.	Casts. No. per 12 hours.	Red cells, No. per 12 hours	White and epithelium cells, No. per 12 hours.
1923 . . .	330	14,600	49,500	247,500
1926 . . .	565–1864	212,000	0	4,180,000

FIG. 3.—Arteriosclerotic Bright's disease with a later complicating degenerative lesion.

The data given in Fig. 3 illustrate this occurrence. The patient died from cardiac decompensation in 1926. In 1918 a slight proteinuria and a mild hypertension were observed. By 1923 the blood pressure had risen to high levels. The observations made at that time showed a slight proteinuria and cylinduria but the number of red blood cells and of white blood and epithelial cells was within normal limits and he was classified as an instance of arteriosclerotic Bright's disease. But in 1926, when cardiac decompensation had occurred, the urinary findings were radically altered. The rate of protein and of cast excretion was much greater, the absolute number of epithelial and granular casts was very large, and the rate of white blood- and epithelial-cell excretion was greatly increased. This was regarded as evidence of the existence of an active degenerative renal lesion. Dr. Oliver's summary states that "The arteries of the kidney show a marked arteriosclerosis. In the kidney tissue there is a moderate fibrosis of the cortex with a slight atrophy of the glomeruli and tubules which are enclosed in the scars. There is also a general parenchymatous degeneration of the epithelium of the convoluted tubules. No active inflammation is present in any of the elements of the kidney."

I. NATURE AND INTENSITY OF RENAL LESION.

Protein, mgs. per 12 hours.	Cast excretion, No. per 12 hours.	Differential				Cast count		
		blood.	epith.	gran.	fatty.	waxy.	hyaline.	renal failure.
1840 to 3900	807,000	0%	0%	0%	3%	0%	98%	0%

Red blood cells, No. per 12 hours.	White and epithelium cells, No. per 12 hours.
0	27,200,000

II. EXTENT OF RENAL LESION.

Not measurable with accuracy.

Blood-urea concentration varied from 76 mg. per 100 cc. when first seen to 60 mg. per 100 cc. shortly before death.

FIG. 4.—Degenerative Bright's disease of unknown etiology. (Volhard and Fahr's "genuine nephrosis.")

The cases grouped under the heading degenerative Bright's disease are patients suffering from diseases of very diverse etiology. There are the transient slight increases in the rate of protein, cast and particularly of epithelial-cell excretion which accompany many acute infections. There is the equally transient but much more pronounced proteinuria and cylinduria associated with the toxemia of late pregnancy.[21] There is the often fatal necrosis of the con-

voluted tubules which occurs in corrosive sublimate poisoning. These are all short-lived lesions which from the point of view of the urinary picture come under the heading degenerative because there is evidence of the desquamation of degenerated renal cells without any or only a slight increase in red blood-cell excretion. But there are also the cases of chronic suppuration in whose urine evidences of a continuing degenerative renal lesion have been observed over long periods of time. And finally there is that much discussed but etiologically still quite obscure condition called "genuine nephrosis" by Volhard and Fahr. The numerical results in a case of this type are given in Fig. 4.

These figures cannot convey the picture seen under the microscope, the shining fat droplets in the hyaline casts, the doubly refractile globules and coarse granules within the epithelial cells. Yet in themselves these peculiarities are not distinctive, for just such appearances are frequently seen in the active stages of hemorrhagic Bright's disease. It is a negative fact, the absence of any increase in red blood-cell excretion, which singles this case out as belonging to the degenerative group.

The patient was a man aged fifty years who for no discoverable reason became edematous. Although he was under observation for four and a half months we could not determine the extent of the renal lesion because it was impossible to induce diuresis. It was very difficult to get him to eat enough and in spite of every effort he took less and less and finally seemed to die of inanition.

Dr. Oliver's summary reads: "The only lesions of any significance in the kidneys are degenerative. There is a severe widespread cloudy swelling and a scattered fatty degeneration of the convoluted tubules. There is no evidence of any inflammatory process."

Finally we come to the group of cases which are characterized by an increase in the rate of red blood-cell excretion. This is clinically the really important group for it is here only that the lesion in the kidney itself may so develop as to become a menace to life. It is in this group also that our present narrow mode of approach finds most scope, since here we have as time passes the greatest change in the evidences from which we try to deduce alterations in the extent and nature of the renal lesion. The single thread which connects all the diverse manifestations observed in this group is an increase in the rate of excretion of red blood cells. Now it will of course at once be objected that hematuria is a sign of very uncertain significance and that even when it is accompanied by an increase in the rate of protein and of cast excretion the origin as well as the meaning of the bleeding must remain a matter of conjecture. This is logically true but nevertheless there are certain peculiarities about the hematuria of these patients which cannot be expressed in numbers or even clearly described in words, peculiarities which differentiate red blood cells which have come from the kidney from those which have come

from other locations in the urinary tract. In this group of patients the red blood cells are usually pale and indistinct, often little more than the shadows of red blood cells, a circumstance which while it is characteristic makes enumeration difficult. And I think in all cases of hemorrhagic Bright's disease at certain stages of their development the urine contains casts which either contain recognizable red blood cells or the deep orange-colored clumps and granules which are formed by the fusion of red blood cells. From these blood casts we may legitimately infer that blood is coming from the kidney itself.

The typical initial and early latent stages of hemorrhagic Bright's disease are illustrated in Fig. 5.

Days from onset.	Extent of lesion. Functioning tissue, per cent of normal.	Nature and intensity of lesion. Protein, mg. per 12 hours.	Cast, per 12 hours.	Red blood cells, per 12 hours.	White and epithelium cells, per 12 hours.
1	(15%)	2400	1,190,000	625,000,000	57,000,000
27		610	330,000	675,000,000	59,000,000
32	68%	511	390,000	225,000,000	13,000,000
37		695	252,000	195,000,000	13,000,000
55		324	208,000	176,000,000	5,400,000
96		65	33,300	85,000,000	4,700,000
117		29	19,100	68,000,000	1,210,000
154		12	27,200	40,000,000	1,400,000
155	Died suddenly from thrombosis of a coronary artery.				

Postmortem Summary. The kidneys show only slight lesions which consist of (1) traces of a former glomerulitis of the intracapillary type and (2) a moderate arteriosclerosis of the renal arteries with slight scarring of the cortex.

FIG. 5.—The initial stage of a hemorrhagic Bright's disease with a sudden cardiac death early in the latent stage.

This patient was a man, aged forty-five years, who developed edema, hypertension and gross hematuria eighteen days after the onset of a cellulitis and lymphangitis of the hand and arm. He was seen at the commencement of the renal lesion and died suddenly from coronary thrombosis 155 days after its onset and on the day after the last urinary measurements were made. The figures indicate the initial intensity of the process and its subsidence within a comparatively short time to a stage where routine urinary examinations would probably have failed to detect any noteworthy abnormality.

Dr. Oliver reports that "The kidneys show only slight lesions which consist of (1) traces of a former glomerulitis of the intracapillary type and (2) a moderate arteriosclerosis of the renal arteries with slight scarring of the cortex. The moderate number of casts, including an occasional blood cast, show that the process is not entirely quiescent."

In the second case of hemorrhagic Bright's disease the patient was a physician with whom I was closely associated from 1918 until his death in 1924. In Fig. 6 I have tried to give a continuous picture of the probable course of the renal lesion.

The upper portion gives the extent and the lower portion is intended to convey the degree of intensity of the lesion. In 1913 he had a severe tonsillitis which was not improbably due to the Scarlatinal streptococcus. The dotted lines are hypothetical and merely represent what usually happens at the commencement of the disease. During the next three years routine urine reports showed that small amounts of protein and a few casts were usually though not constantly present. In 1916, he had a fever of unknown origin for a few days and for some weeks thereafter considerable number of red blood cells as well as protein and casts were reported. In the fourth year

from the onset he contracted a fever while on a troop train on which an outbreak of tonsillitis occurred. He had a gross hematuria on this occasion, but three weeks later routine examination failed to disclose any urinary abnormality. During the fifth and sixth years after the onset I made repeated examinations under the proper conditions and always found an increase in the number of red blood cells and a few blood casts, but quantitative results could not be obtained until the seventh year. At that time 91 per cent of the normal amount of renal tissue was still functioning and the intensity of the lesion was slight. Yet it was known that the lesion had led to a continuous slight bleeding for three years and the history made it probable that this active process had existed for seven years. During the eighth year evidences of a degenerative element appeared. The number of epithelial cells increased, and many of them were filled with fat globules and granules. The rate of protein excretion markedly increased, large numbers of casts appeared and they were sprinkled over with fat droplets. At the same time the urea-ratio measurements showed a progressive decrease in the amount of still functioning renal tissue. In the ninth year the terminal stage began to make its appearance. The amount of renal tissue was only

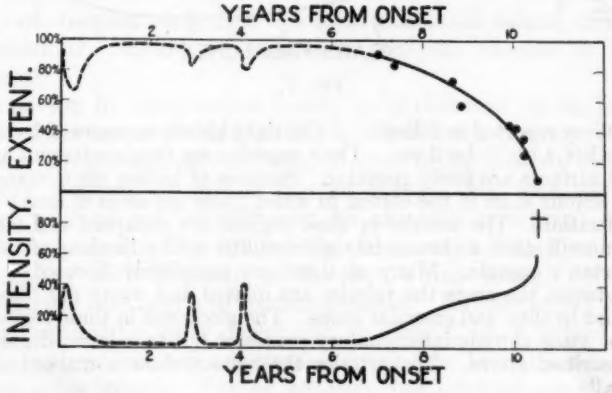


FIG. 6.

38 per cent of the normal, the urine volumes began to increase and small percentages of renal failure casts[22] were found. But this stage was never fully developed for an acute gastrointestinal disorder led to dehydration and precipitated the uremia from which he died.

Dr. Oliver's report is as follows: "The kidneys were of the usual size. Sections show a very active glomerulitis of both the intra- and extracapillary type involving practically every glomerulus. There is a diffuse scarring with cellular connective tissue throughout the cortex and a resulting atrophy of the majority of the convoluted tubules. The epithelium of those still intact shows fatty degeneration and cloudy swelling. There are many casts of all types in all the tubules. The arteries show no significant lesion."

The last case I shall instance is shown in Fig. 7.

This was a young woman, aged twenty-one years, who remained at work and quite unconscious of any illness until a month before the end in spite of the fact that she had a very extensive renal lesion. The graph shows the slow but relentless progression of the lesion. The dots represent urea ratios and the circles are the prediction as to the amount of renal tissue derived from the blood-urea concentrations in accordance with the average relationship which Dr. E. M. MacKay and Dr. L. L. MacKay[23] found between the

urea ratio and the blood-urea concentration when more than half the renal tissue is gone. It will be observed that in this case the intensity of the lesion was always low, although even three years before her death the presence of renal failure casts indicated the gravity of the prognosis.

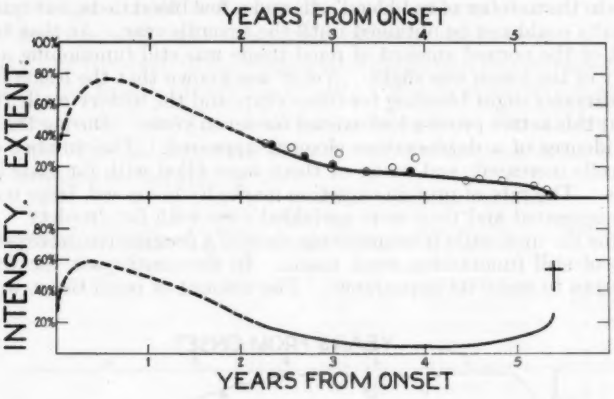


FIG. 7.

Dr. Oliver reported as follows: "The right kidney measures 8 by 4 by 2½ cm.; the left 4 by 2½ by 2 cm. Their capsules are firmly adherent and the external surfaces are finely granular. Sections of kidney show many large cellular fibrous scars in the cortex, in which there are areas of heavy round-cell infiltration. The tubules in these regions are collapsed and atrophic. The glomeruli show a chronic intraglomerulitis with adhesions of the tufts to Bowman's capsule. Many of them are completely fibrosed. In the areas between the scars the tubules are dilated and many are filled with debris and hyaline and granular casts. The glomeruli in these regions also show the same chronic inflammatory processes but to a lesser degree than were described above. The arteries throughout show a marked arteriosclerosis."

What then have we found as a result of such observations? We have found: (1) That by a study of the urine patients with Bright's disease may be divided into three groups to which the names arteriosclerotic, degenerative and hemorrhagic Bright's disease have been provisionally attached. (2) From the 75 instances in which the urinary observations were compared with the renal lesion as it existed at the moment of death, we have found that the arteriosclerotic group are characterized by an arteriosclerosis of the renal arteries and by a patchy fibrosis of the cortex; that the degenerative cases show granular, fatty or necrotic changes in the tubule cells, while the hemorrhagic group are distinguished by the presence of inflammatory lesions in the glomeruli. As a result a classification which was at first only a summary statement of the observation that some kidneys bled, others excreted an excess of degenerated cells, and still others neither bled nor desquamated cells, begins to acquire an anatomic significance. We now have evidence that

bleeding means an active glomerular inflammation, that an increased excretion of epithelial cells means tubular degeneration, and that a continuing slight excess of casts and protein and cells in the urine may mean a renal arteriosclerosis.

So far the bare original hypothesis with which we started has been confirmed, and to this extent we can use it in the investigation of the next question which presents itself, the question as to whether the separations made by counting the formed elements of the urine have any *permanent* significance. May a kidney at one time bleed, at another time show evidence of degeneration and yet later be classified as falling within the arteriosclerotic group? Or does a hemorrhagic case run true to form throughout its entire course, does a degenerative case continue always to show evidences of degeneration and does an arteriosclerotic lesion remain constant? In other words is Bright's disease a pathologic unity although it manifests itself in different forms, or is Bright's disease simply a convenient name for a group of diseases each with its own individual origin, course and termination? Should we talk about Bright's disease or Bright's diseases?

An answer to this question is only to be obtained by the long continued observation of many patients. But it is a clear question and we have simple clinical methods, so that in the end we shall know whether Bright's disease is one or many. My own experience, though perhaps not yet sufficient for any objective proof, has thus far strongly inclined me toward the view that in Bright's disease we are dealing with a group of diseases which though related are individually constant and distinguishable. But obviously the final answer cannot be quite direct and simple. I have indeed already cited a patient classed as arteriosclerotic who later passed into the degenerative group. Yet at autopsy the original arteriosclerotic as well as the terminal degenerative lesion was found. Here we had the coëxistence of two types of lesion. Again in the second instance of the hemorrhagic group which I summarized we have for five years a purely hemorrhagic lesion and then in addition the manifestations of an active degeneration. But it should be noted that the lesion nevertheless remained hemorrhagic throughout its entire course and clinically distinguishable from any purely degenerative case. Through all cases of hemorrhagic Bright's disease runs the record of an increase in the rate of red blood-cell excretion and this I believe unites them together as examples of one disease in spite of the presence or absence of degeneration and in spite of the great differences in their clinical course and final pathology.

The observations thus far, then, tend toward the conclusion that the hemorrhagic cases through all their diverse stages are one disease; that the arteriosclerotic cases are another and quite separate disease, and that in the degenerative group we are dealing with the renal effects of many different diseases. There is nothing new in this, it

is in fact the conclusion which most pathologists and almost all clinicians have already reached on the basis of much broader and more ample evidence than these methods can ever supply. Yet if this should prove to be the final outcome, the result will still hold its place in the completed structure of the theory of Bright's disease by virtue of the fact that this conclusion will rest solely on objective quantitative data derived from every stage in the evolution of the renal lesion from the beginning to the end.

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RENAL FUNCTION IN ARTERIAL HYPERTENSION.*

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The generally accepted criterion for the diagnosis of essential hypertension is the presence of a persistent elevation of blood pressure without renal impairment. For many years, it will be recalled, all patients with hypertension were diagnosed as Bright's disease and it was not until quite recently that a group of hyperten-

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sives was sharply differentiated from the nephritics, because a study of their blood chemistry showed no evidence of nitrogen retention and tests of kidney function gave normal results. Most students of hypertension divide it somewhat arbitrarily into two groups, the hypertension of nephritis and essential hypertension—the latter diagnosis being usually a term applied to hypertension in which there is no clear evidence of renal insufficiency. While it is universally admitted that certain cases of so-called essential hypertension may later develop renal insufficiency and die a renal death, the

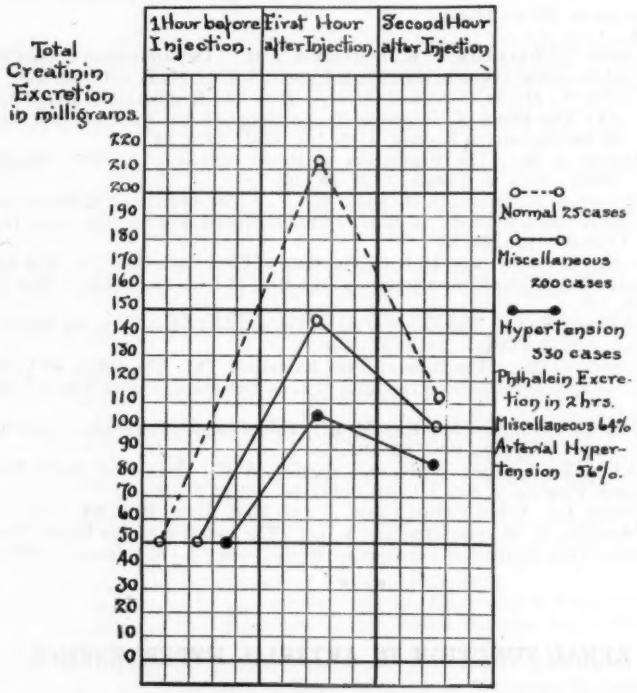

FIG. 1.—Results of creatinin test in 25 normal individuals, in 200 patients suffering from various diseases and in 330 cases of arterial hypertension. No case of nephritis included.

majority of them show at no time evidence of serious renal disease and die from cardiac failure, apoplexy or other causes. In Janeway's[1] carefully studied series, approximately one-fourth died later of renal insufficiency, a complication frequently delayed ten years or even longer.

In the earlier stages of all cases of essential hypertension and throughout the course of most of them, there is no evidence of nitrogen retention in the blood. There may be one exception to this in the high blood uric acid values which are frequently encountered in

essential hypertension, to which Kraus,[2] Fishberg and others called attention. Fishberg,[3] however, had an opportunity of studying the kidneys in four of his patients with high blood uric acid and found no evidence anatomically of renal insufficiency. Fishberg thinks "the increased uric acid content of the blood is due to metabolic causes and not to beginning renal insufficiency," a conclusion that seems justified by the evidence at hand.

There is, however, general agreement that the blood nonprotein nitrogen, urea and creatinin are not increased in essential hyperten-

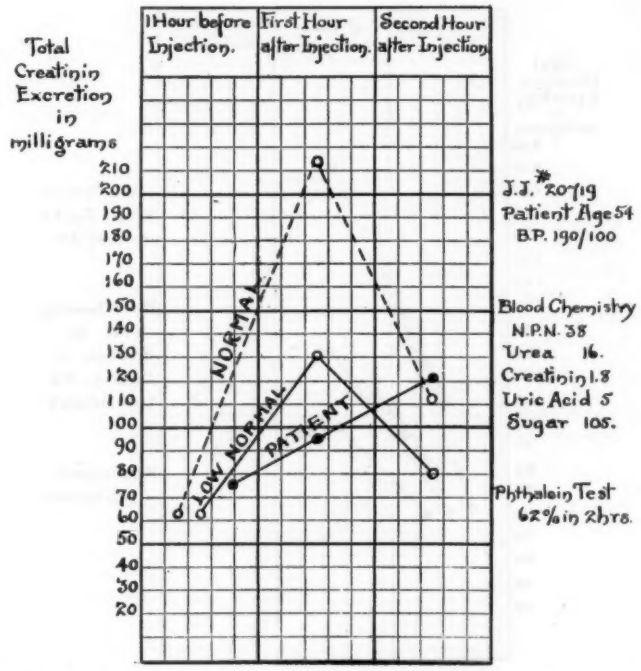

FIG. 2.—Results of creatinin test in hypertensive patient, J. J. Curves of average and low normal superimposed.

sion and the majority of observers find there is no evidence of renal insufficiency in spite of the presence of albumin and casts in the urine of the patients. The test for renal function which is almost universally employed is the well-known phenolsulphonephthalein test introduced by Rowntree and Geraghty.

In the series of patients which we have studied, the renal function test of Rowntree and Geraghty has been employed and only those patients considered who showed an excretion of not less than 40 to 50 per cent in two hours after intravenous injection. The number of patients studied was 330. Only a small number showed an excre-

tion of less than 50 per cent, the average excretion of phenolsulphonephthalein in these patients being 64 per cent in two hours. None of these patients showed an increase of nonprotein nitrogen, urea or creatinin in the blood. This finding, together with an adequate 'phthalein excretion, would place them in the group of essential hypertensives.

These patients have been studied not only from the standpoint of 'phthalein excretion but have been subjected to the creatinin test for kidney function, which we[4] described in 1923 and which has been

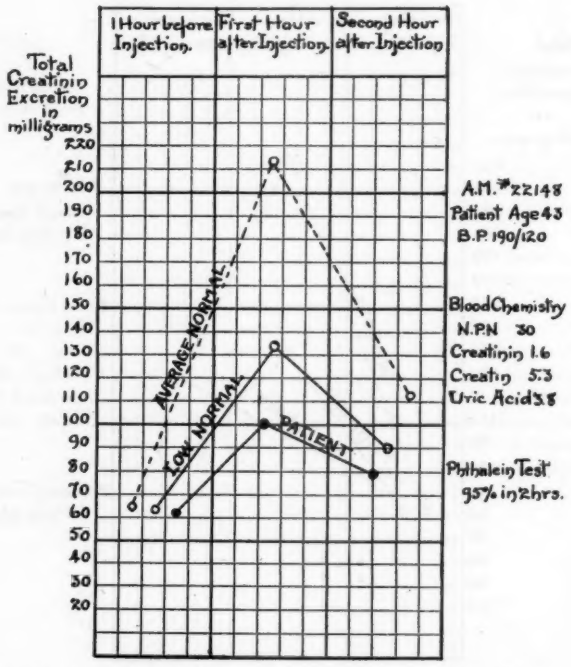

FIG. 3.—Results of creatinin test in hypertensive patient, A. M. Curves of average and low normal superimposed.

employed continuously in our clinic since that time. The creatinin test has been employed simultaneously with 'phthalein in approximately 1000 cases, the creatinin and the phenolsulphonephthalein solutions being mixed and injected together. From these findings, we have formed certain ideas regarding the excretion of creatinin in health and in disease.

The creatinin test is carried out by collecting the urine for one hour, then injecting intravenously 0.25 gm. of creatinin in a buffer solution and studying the excretion of creatinin for the first hour and the second hour after injection. The amount of creatinin excreted

in the urine during the first and second hours after injection, is compared with the creatinin content of the urine before injection.

In Fig. 1 are shown the results obtained with the creatinin test in 25 normal individuals, in 300 patients suffering from various diseases without evidence of renal disease and with normal blood pressure, and in 330 patients suffering from essential hypertension.

We have found that the great majority of normal individuals excrete three times as much creatinin in the first hour as during the control hour before injection, but because of the fact that some

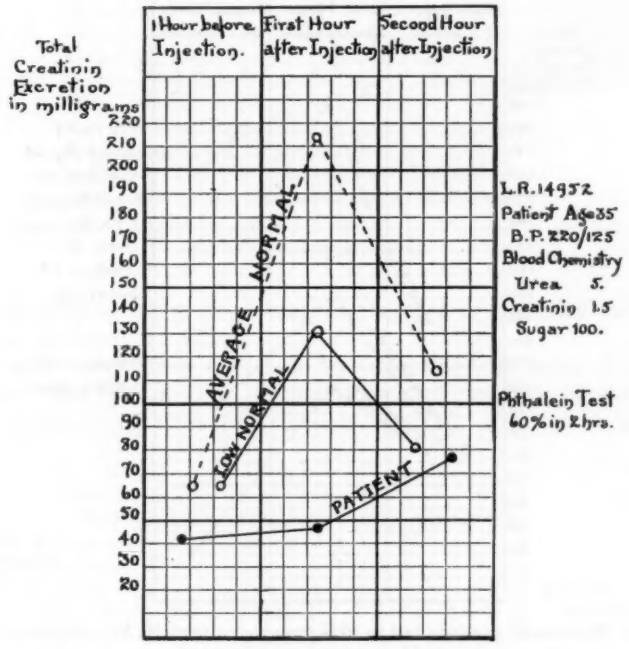

FIG. 4.—Results of creatinin test in hypertensive patient, L. R. Curves of average and low normal superimposed.

individuals with no evidence of kidney lesions excrete only twice as much, we have taken this latter figure as the low level of normal response.

In comparing the results of the tests in the group of essential hypertension, their average excretion of creatinin is decidedly lower than in the controls. Many of the patients, the exact number being 200, showed a normal excretion of creatinin and some of the patients, especially those in whom the arterial hypertension was complicated by diabetes mellitus, showed a very high excretion of the creatinin. The inclusion of patients having a normal excretion of creatinin has,

of course, raised the average of creatinin excretion in the group of hypertensives.

One hundred and thirty of the cases of arterial hypertension, or 39 per cent, showed an excretion of creatinin well below the normal values. In many patients, such as shown in Figs. 2, 3, 4 and 5, the excretion of creatinin was far below the normal. These results are particularly striking when we consider that these patients had a normal blood nonprotein nitrogen, urea and creatinin and showed a normal phenolsulphonephthalein excretion.

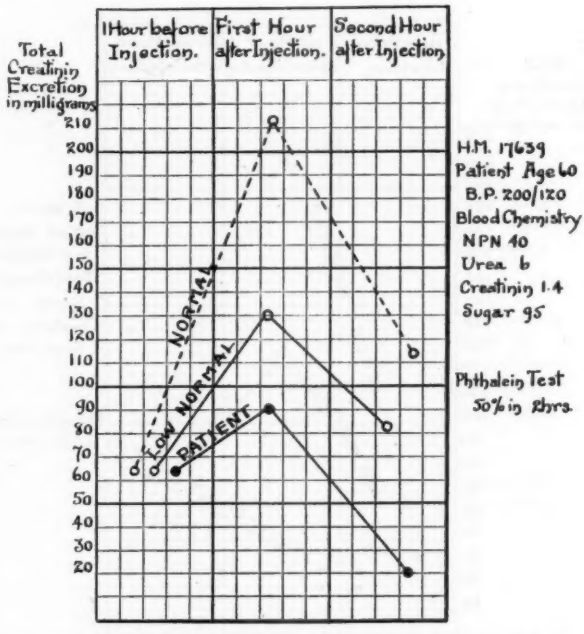

FIG. 5.—Results of creatinin test in hypertensive patient, H. M. Curves of average and low normal superimposed.

These results, we believe, justify the conclusion that many patients with arterial hypertension who have a normal blood chemistry, as the term is generally employed, and who have an adequate kidney function when studied by the usual method, show evidence that the kidney is not functioning normally so far as the excretion of creatinin is concerned. It also indicates to us that in hypertensives the creatinin test for kidney function is more sensitive than the phenolsulphonephthalein test.

We have also employed another test of kidney function, the ability of the kidney to excrete methylguanidin. This test employs the method for the estimation of guanidin in the urine recently devised by Weber. Leaving aside for the present, the question as

to whether methylguanidin occurs normally in urine, we will say that when this method is employed, normal urine gives a color that can be read quantitatively and when small amounts of methylguanidin are injected subcutaneously or intravenously, taken by mouth or

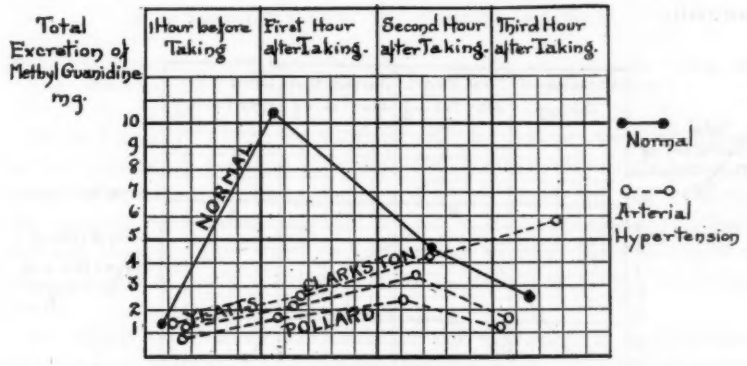

FIG. 6.—Excretion of methyl guanidine in 3 patients with arterial hypertension compared with normal curve.

added directly to the urine, a marked increase in the color value of the urine is obtained.

We have carried out this test by collecting the urine first for one hour, then giving 50 to 100 mg. of methylguanidin sulphate by mouth on an empty stomach and then collecting the urine in hourly

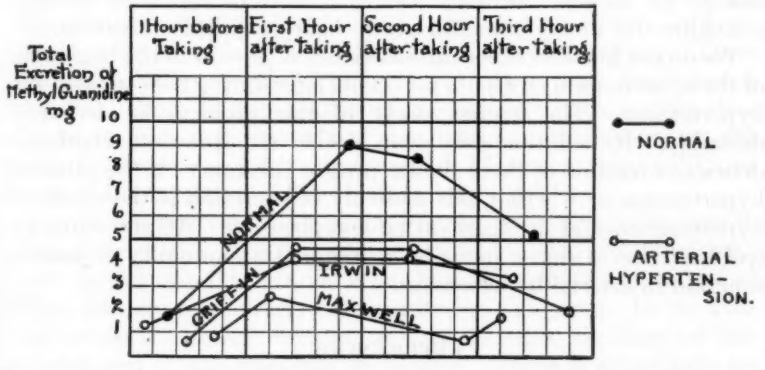

FIG. 7.—Excretion of methyl guanidine in 3 patients with arterial hypertension compared with normal curve.

periods for three hours. In making comparisons of excretion, patients are grouped together who have taken the same amount of methylguanidin. These tests have been carried out on a comparatively small number of persons, 10 normal controls and 30 hyper-

tensives, but the differences have been very striking. Some of the results obtained are shown in Figs. 6, 7 and 8.

These results indicate that certain hypertensives, again presumably with normal blood chemistry and kidney function, when tested by the usual methods, do not excrete methylguanidin normally.

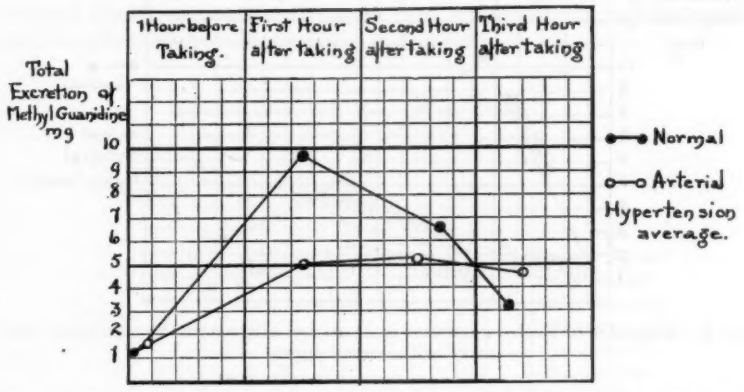

FIG. 8.—Average excretion of methyl guanidine in 10 normal individuals with normal blood pressure and in 30 cases of arterial hypertension.

Conclusions. The results of our observations indicate that many hypertensives belonging to the group of essential hypertension, do not, as commonly stated, have a normal kidney function. They are unable to excrete normally two guanidin compounds, methylguanidin and methylguanidin acetic acid anhydride (creatinin).

We do not know whether this deficiency is present in the beginning of the hypertension or whether it occurs later during the course of the hypertension. The further study of this problem is obviously desirable. Its solution may help decide the question whether a deficient excretion of these similar pressor substances is the cause of hypertension or whether this anomaly of excretion is the result of hypertension, and an aggravating complication. At any rate, we feel that this evidence indicates a frequent abnormality of kidney function in arterial hypertension.

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ACUTE MERCURIAL INTOXICATION.

Report of Thirty-eight Cases.

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From January 1, 1926, to April 5, 1927, 38 patients were admitted to the Cincinnati General Hospital with a diagnosis of acute mercurial intoxication. Thirty-seven stated bichlorid had been taken. One patient had taken calomel for therapeutic purposes. Three claimed that the mercurial was taken by mistake and 34 made a frank avowal of suicidal intent. In all cases, the drug was taken by mouth.

In exactly one-half of the cases the signs, symptoms and laboratory findings manifested during the hospital stay were not indicative of mercury poisoning. For the purpose of this study, the cases were divided into two groups, the clinically proven cases being listed on Chart I under the heading of "Mercurial Intoxication" while the doubtful cases are shown on Chart II under the title of "Suspected Mercurial Poisoning."

On Chart I are listed 18 cases of bichlorid poisoning with five deaths, making a mortality rate of 28 per cent. In this fatal group all were white. Four autopsies were performed.

The Dose. The largest dose recorded in this series is 37.5 gr. The smallest dose on Chart I is 7.5 gr. and on Chart II, 3 gr. Death occurred with 37.5, 30, 22.5 and 15 gr. respectively. There were no fatalities in the 7.5 gr. group. The average fatal dose is 28.3 gr. There is apparently no relationship between the dose alleged to have been taken and the symptoms manifested by the patient. Severe cases were produced by 7.5 gr. and very mild ones followed the ingestion of five times as much.

The Emesis Interval. The emesis interval is defined as the time in minutes from the ingestion of the poison to the first vomiting.[1] In the fatal group this interval is one hundred and twenty, sixty and fifteen minutes respectively and is unknown in 2 cases. In the nonfatal group the longest interval was ten minutes, the shortest two minutes and it was unknown in 3 cases. There is apparently no relation between the emesis interval and the severity of the disease, although there appears to be a very definite relation between the emesis interval and the mortality.

In the suspected cases, the emesis interval is exceedingly short in all patients in whom the history may be believed. In several patients admitting to a long emesis interval, the total absence of

CHART I.—MERCURIAL POISONING, CINCINNATI GENERAL HOSPITAL, 1926–1927—CASE HISTORIES.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Summary.
1. Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
2. Name	A. S.	M. R.	M. S.	M. F.	E. H.	B. C.	M. C.	H. H.	C. C.	J. P.	E. P.	S. F.	A. C.	V. M.	H. K.	C. S.	H. B.	E. F.	A. S.	19
3. Age	20	48	22	56	38	30	36	23	34	23	19	15	36	29	27	30	28	22	83	
4. Sex	F.	F.	F.	M.	F.	F.	F.	F.	F.	F.	F.	F.	F.	F.	M.	M.	F.	F.	M.	15 F. 4 M.
5. Color	W.	W.	W.	W.	W.	B.	W.	B.	W.	W.	W.	W.	W.	W.	W.	B.	W.	W.	W.	16 W. 3 B.
6. Civil status	Sgle.	Md.	Sgle.	Div.	Md.	Md.	Md.	Div.	Md.	Md.	Md.	Sgle.	Md.	Wid.	Md.	Md.	Md.	Md.	Wdr.	12 Md. 3 Sgle.
7. Occupation	None	Hswf.	None	Ptr.	Hswf.	Maid	Hswf.	Maid	Hswf.	Hswf.	Watrs.	Stud.	Clerk	None	Agt.	Port.	Wtrs.	None	Paper	
8. Alleged dose, in grains	37.5	15	37.5	30	22.5	22.5	30	30	22.5	7.5	7.5	7.5	7.5	15	15	37.5	22.5	15	12HgCl	
9. Emesis interval, in minutes	15	60	Unkn.	120	Unkn.	5	2	2	Unkn.	2	2	5	10	Unkn.	2	Unkn.	10	2	None	
10. Course	Fatal	Fatal	Fatal	Fatal	Fatal	Severe	Mod.	Mod.	Mod.	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Severe	
11. Hospital stay, in days	11	4 hrs.	10	2	9	26	15	16	9	43	10	10	9	6	4	2	9	1	19	
12. Signs and symptoms	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19
A. Alimentary:																				
a. Burning and pain in mouth	+	...	...	+	++	...	...	++	...	...	...	...	...	...	...	++	...	...	...	5
b. Metallic taste	++	...	...	...	++	...	...	...	...	...	...	...	...	...	...	...	...	...	+++	3
c. Salivation	+++	...	...	...	+++	+++	...	...	...	...	...	...	...	...	...	...	...	...	+++	4
d. Vincent's angina	++	...	++	...	++	++	...	...	...	...	...	...	...	...	...	...	...	...	+++	5
e. Mercurial line	...	...	...	++	...	...	...	...	...	+	...	...	...	...	...	...	...	...	+++	3
f. Fetor oris	+++	...	+++	...	+++	+++	...	...	+++	...	...	...	...	...	...	...	...	...	+++	6
g. Stomatitis	++	...	++	...	+++	++	...	...	++	+	...	++	...	...	...	+	++	...	+++	10
h. Gingivitis	++	...	+	+	++	++	...	...	+++	+	...	...	...	...	...	...	...	...	+++	8
i. Pharyngitis	++	...	++	+	++	++	...	...	+++	+	...	...	...	...	++	...	...	++	...	9
j. Nausea	+++	+	+++	...	+++	++	++	++	++	+	...	...	++	++	++	...	...	...	++	13
k. Retching	+++	...	+	...	+++	...	...	...	...	+	...	...	+	...	...	...	...	...	...	5
l. Vomiting	+++	+	++	...	+++	++	++	++	++	+	...	...	++	++	+++	...	...	...	+	13
m. Hematemesis	+++	...	++	...	+++	++	++	+	++	...	...	...	...	+	...	...	...	...	...	8
n. Epigastric tenderness	++	+	++	...	++	...	...	...	...	+	...	++	...	+	...	...	...	...	...	7
o. Right costal tenderness	++	++	++	...	++	...	...	...	...	...	+++	...	...	++	...	...	+++	...	...	7
p. Abdominal tenderness diffuse	+++	...	++	+	++	...	...	...	+++	...	...	...	...	+++	+++	...	+++	...	...	8
q. Epigastric pain	+++	+	+	...	++	...	...	...	++	...	...	...	...	+	+++	...	...	...	...	7
r. Abdominal pain diffuse	+++	...	+	+	++	...	...	...	+++	...	...	...	...	+++	...	...	...	...	...	6
s. Gastritis	+++	...	++	+	+++	...	...	...	++	...	...	...	...	++	...	...	...	...	...	6
t. Enteritis	+++	...	++	+	+++	...	...	...	++	...	...	...	...	++	...	...	...	...	...	6
u. Cramps	+++	...	+	...	+++	+++	...	...	++	...	...	...	...	++	...	...	...	...	...	6
v. Tenesmus	+++	+	+	...	+++	...	...	...	++	...	...	...	...	...	...	...	+++	...	...	6
w. Diarrhea	+++	...	++	+	+++	...	++	...	+++	+	...	...	++	++	...	+	...	...	...	10
x. Melena	+++	...	++	+	+++	...	+	...	...	...	...	...	...	++	...	...	...	...	...	6
y. Fecal incontinence	++	...	+	...	+++	...	...	...	...	...	...	...	...	...	...	...	...	...	...	3

x. Melena																				
y. Fecal incontinence	++	...	+	...	+++	...	...	...	...	...	...	...	...	...	...	...	...	...	...	
B. Urinary:																				
a. Incontinence	+++	...	++	...	+++	...	...	...	...	...	...	...	...	...	...	...	...	...	...	3
b. Oliguria	+++	...	+++	+	+++	++	...	...	...	++	...	...	...	...	...	...	...	...	...	6
c. Anuria, in days	...	...	+4	+	++	+4	...	...	...	...	...	+1?	...	...	...	...	...	...	...	5
C. Cardiovascular:																				
a. Blood pressure	98/60	Unkn.	88/55	Low	135/70	Unkn.	100/70	94/54	135/64	125/80	104/58	102/70	100/54	Unkn.	100/60	132/92	95/60	105/80	90/60	
b. Pulse	100	88	95	120	96	104	76	120	96	104	102	74	108	108	80	80	80	100	80	
c. Respiration	20	...	26	32	20	24	20	20	20	24	30	20	24	20	20	24	24	24	20	
d. Temperature	99.4	...	100	100	100	97	98	97	98	98.6	98.6	98.6	97.8	99	98	98	98.6	97	103	
D. Visceral:																				
a. Kidney—nephrosis	+++	...	+++	++	+++	+++	...	++	...	+	+	...	...	...	...	...	...	+	+	10
b. Liver	++	+2f.b.	...	...	++	...	+	...	...	...	...	...	...	...	...	...	+	...	...	5
E. Psyche	....	...	Del.	Irrat.	...	Manic	...	...	...	...	...	...	...	Paran.	...	...	...	...	...	4
F. Associated pathology:																				
a. Drunkenness	....	...	...	+++	++	...	++	++	...	...	...	++	...	...	++	...	++	...	...	7
b. Syphilis	....	...	...	...	...	...	+	+	...	...	...	...	...	...	...	...	...	...	...	2
c. Chronic nephritis	....	...	...	++	...	...	...	...	...	++	...	...	...	...	...	...	...	...	+++	3
d. Focal infection	....	...	...	++	...	...	...	+	...	...	...	...	+	...	...	...	...	...	...	4
13. Laboratory Findings:																				
A. Blood—Wassermann	Neg.	Unkn.	Neg.	Unkn.	Neg.	Neg.	Neg.	+++	Unkn.	Neg.	Neg.	Neg.	Neg.	Unkn.	Neg.	Unkn.	Unkn.	Unkn.	Unkn.	10 Neg. 1 Pos.
Count—R. B. C., in thousands	5,400	...	4,000	...	4,120	4,450	4,200	4,500	4,800	3,680	4,814	3,900	3,648	4,800	4,300	....	3,790	4,700	4,300	
W. B. C.	11,000	...	22,000	...	8,400	7,600	16,000	10,700	11,000	10,400	9,600	15,600	8,600	12,700	6,200	13,200	12,200	9,600	11,300	
Hgb.	95%	...	85%	...	80%	85%	80%	80%	85%	85%	85%	90%	95%	85%	...	...	...	80%	80%	
Chemistry—Urea N, in mg.	23	...	36	...	46	31	15	...	8	44	13	8	11	15	11					
CO_2	48	...	29	...	...	40	54	...	...	...	60									
Mercury estimation	....	...	...	...	5 mg.%	...	3 mg.%													
B. Urine—Albuminuria	++	...	+++	...	+++	+++	Neg.	++	Neg.	+++	Trace	+++	+	+++	++	...	Neg.	Trace	++	11 Pos. 3 Neg.
Cylindruria	++		++	...	++	++	...	++	...	...	...	+	...	...	++	...	...	...	...	7
Hematuria	++	...	++	...	+++	++	...	+++	...	++	...	...	...	++	++	...	...	...	++	10
Pyuria	++	...	++	...	+	++	...	...	...	++	...	...	...	...	...	...	...	...	...	5
P. S. P., completed	....	...	...	...	15%	...	50%	50%	9%	28%	...	27%	20%	...	...	...	...	...	...	7
C. Stool	Blood	...	Blood	...	Blood	...	Blood	...	Blood	...	Blood	...	...	Blood						
	+++	...	+++	...	+++	...	+++	...	++	...	++	...	...	+++						
D. Lavage	Blood	...	Blood	...	Blood	Alc.	Alc.	Alc.	...	...	...	...	...	...	Blood	...	...	...	...	4 Blood
	++	...	++	...	++	+++	+++	+++	...	...	...	...	...	...	++	...	...	...	...	3 Alc.
14. Treatment																				
A. Expectant	+	...	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	...	17
B. Active	+	+	+	+	+	+	+	+	+	+	+	...	+	+	+	+	+	+	...	17
Infusions—Glucose and saline, cc.	16000	...	13000	...	2900	1800	...	...	...	...	...	...	...	...	...	...	...	...	...	4
Intravenous—	+	+	+	+	+	+	+	+	+	+	+	...	+	+	+	+	+	+	+	18
Fischer's solution, cc.	2600	1200	2900	3000	4300	3150	1350	1700	1100	3400	1000	...	1500	1500	1700	...	1000	1500	...	16
Sodium thiosulphate	....	...	...	...	2 gm.	...	1 gm.	...	...	1 gm.	...	...	...	...	...	7 gm.	...	...	45 gm.	5
Glucose, cc.	1500	...	3300	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	2
Miscellaneous	$NaHCO_3$ Intrav.	...	Decap.																	

CHART II.—SUSPECTED MERCURIAL POISONING, CINCINNATI GENERAL HOSPITAL, 1926–1927—CASE HISTORIES.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Summary.
1. Case number																				19
2. Name	B. C.	M. H.	B. C.	M. C.	B. F.	M. W.	C. L.	G. N.	L. R.	E. N.	T. F.	J. N.	C. K.	J. H.	D. M.	B. R.	H. R.	M. S.	R. A.	
3. Age	30	22	15	40	43	26	23	26	26	27	22	30	25	48	30	29	15	24	32	
4. Sex	F.	F.	F.	F.	F.	F.	F.	M.	F.	F.	F.	M.	F.	M.	F.	M.	F.	F.	F.	4 M. 15 F.
5. Color	B.	W.	W.	W.	W.	W.	W.	W.	B.	W.	W.	W.	W.	W.	W.	W.	W.	W.	W.	17 W. 2 B.
6. Civil status	Md.	Md.	Sgle.	Md.	Md.	Md.	Md.	Wdr.	Md.	Md.	Md.	Md.	Md.	Md.	Md.	Md.	Sgle.	Md.	Md.	16 Md.
7. Occupation	Maid	Clerk	Stud.	Fact.	Hswf.	Assem.	Wtrs.	Mech.	Ldrs.	Hskpr.	Hskpr.	Mech.	Hswf.	Eng.	None	Driver	Stud.	Hswf.	Unkn.	
8. Alleged dose in grains	15	7.5	3.5	7.5	Unkn.	7.5	7.5	30?	7.5	3	10?	30?	7.5	3	Unkn.	15	5	7.5	7.5	
9. Emesis interval, in minutes	5	2	2	Unkn.	2	2	2	Unkn.	15	2	Unkn.	2	2	5	Unkn.	Unkn.	10	30?	None	
10. Course	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	
11. Hospital stay, in days	3	6	3	5	7	10	1	2	10	2	1	4	1	4	1	1	10	5	1	
12. Signs and symptoms	+	+	+	...	+	+	+	+	...	...	+	...	+	+	...	...	+	+	+	13
A. Alimentary:																				
a. Burning and pain in mouth	....	...	...	...	+++	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
b. Stomatitis	....	+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
c. Pharyngitis	....	...	...	...	++	...	...	...	...	...	...	...	...	+	...	...	...	...	+	3
d. Nausea	++	++	++	...	++	++	++	++	...	...	+	...	++	+	...	...	++	+	...	12
e. Retching	++	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
f. Vomiting	++	...	++	...	+	...	+	...	...	...	+	...	++	...	...	...	...	...	...	6
g. Epigastric tenderness	+++	...	...	...	+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	2
h. Right costal tenderness	+++	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
i. Diffuse abdominal tenderness	....	...	...	...	...	++	...	...	...	...	...	...	...	...	...	...	...	...	...	1
j. Epigastric pain	....	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	+++	++	...	2
k. Diarrhea	....	...	...	...	...	...	...	+	...	...	...	...	...	+	...	...	...	...	...	2
B. Urinary	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	0

B. Urinary																			
C. Cardiovascular:																			
a. Blood pressure	106/76	Unkn.	120/78	100/60	Unkn.	Unkn.	Unkn.	110/70	130/82	Unkn.	Unkn.	Unkn.	Unkn.	160/80	Unkn.	112/78	80/55	115/75	Unkn.	9
b. Pulse	88	112	104	78	108	70	102	106	80	108	120	82	88	72	95	92	85	90	94	
c. Respiration	24	22	24	20	24	24	20	24	20	24	24	20	20	20	18	22	20	22	24	
d. Temperature	98	98	98.6	99	99	98.8	97.4	99.4	98.6	99	98.8	98	98	98.4	100	99.6	98.6	98	98.4	
D. Visceral:																				
a. Liver	....	+Palp.	....	....	....	....	....	....	+Palp.	....	....	....	....	....	....	....	....	....	....	2
E. Psyche	....	....	Appr.	....	....	Semi-consc.	....	Hyst.	....	Stupor	....	....	Hyst.	....	Semi-consc.	....	....	....	....	6
F. Associated pathology:																				6
a. Drunkeness	++	+++	....	+++	....	....	....	++	....	+++	+++	+++	....	....	+++	....	....	....	++	9
b. Syphilis	....	....	....	....	....	+CNS	....	....	+	....	+	....	+	+	....	....	....	....	....	5
c. Focal infection	....	....	....	++	....	+++	....	....	....	....	....	....	....	++	....	....	....	....	....	3
13. Laboratory findings:																				
A. Blood—Wassermann	Neg.	Unkn.	Neg.	Neg.	Unkn.	+++	Unkn.	Unkn.	+++	Unkn.	++	Neg.	+++	Neg.	Unkn.	Unkn.	Neg.	Neg.	Unkn.	11 Done 4 Pos.
Count, R. B. C., in thousands	4,160	4,500	4,720	4,100	4,400	3,400	....	5,100	5,120	....	....	....	4,200	4,240	....	....	5,400	4,880	5,120	13 Done
W. B. C.	10,600	13,000	9,750	9,200	8,600	10,400	....	8,200	6,300	....	....	....	8,450	6,000	....	....	8,000	15,800	4,800	13 Done
Hgb.	70%	75%	90%	85%	Unkn.	70%	....	80%	70%	....	....	....	80%	90%	....	....	69%	85%	65%	12 Done
Chemistry—Urea N.	16 mg.	10 mg.	11 mg.	....	11 mg.	....	....	21 mg.	....	8 mg.	6 mg.	9 mg.	....	21 mg.	....	....	14 mg.	10 mg.	....	11 Done
Mercury estimation	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	Neg.	Neg.	....	2 Done
B. Urine—Albuminuria	....	....	....	....	....	....	....	....	Trace	....	....	....	....	....	....	....	....	....	....	
P. S. P.	....	....	....	....	....	50%	....	....	....	80%	....	75%	....	....	....	....	....	....	....	3 Done
C. Stool	Neg.	Neg.	Neg.	Neg.	Blood ++	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Blood +	....	2 Pos.
D. Lavage	Food ++	Alc. ++	....	....	....	....	....	Food ++	....	Alc. +++	Alc. +++	Alc. +++	Food +++	....	....	....	....	....	Alc. +	
14. Treatment:																				
A. Expectant	++	++	++	++	+++	++	+	++	+++	+++	++	++	+	++	++	+	++	++	++	
B. Active	+	....	....	....	+	....	....	+	....	....	+	+	....	....	+	....	....	....	....	6
a. Infusions	....	....	....	....	600 cc. Gl															
b. Intravenous	1000 cc. Gl.	....	....	....	700 cc. Fis.	....	....	1100 cc. Fis.	....	....	1000 cc. Fis.	1000 cc. Fis.	....	....	1000 cc. Fis.	....	....	....	....	5 Fis.

symptoms, intoxication, or very grave psychic disturbance throw doubt upon the statements that they had actually received any mercuric chlorid. This is further borne out in several such patients in whom no mercury could be demonstrated in the blood stream.

Course in the Hospital. All cases were received within the first ten hours after having taken the poison. Of the fatal cases, the duration of life after the ingestion of the mercurial ranged from four hours to eleven days. In the group who recovered one remained in the hospital forty-three days and one for only one day. One case was very severe, 2 were moderately severe and 10 were classified as mild. The suspected cases were all very mild.

Signs and Symptoms. Immediate signs and symptoms were referable to the cardiovascular system, manifested by a drop in blood pressure and tachycardia, or to the alimentary canal and shown by vomiting, hematemesis and diarrhea. An elevation of temperature immediately following the initial shock was noted as a very grave prognostic sign in this series. This was also true of a rise in leukocyte count which has been previously noted by other investigators.[3] An inverse curve is described by the blood pressure, the readings showing a continuous drop for the duration of the acute intoxication, rising gradually to normal as the patient's condition improved. The tachycardia noted in the beginning became progressively worse as the disease progressed but cleared up rapidly if the patient recovered. There seemed to be no appreciable effect on the respiratory rate, except during the terminal stage of a fatal toxemia in which extreme air hunger and dyspnea supervened.

Nausea and vomiting were persistent and uncontrollable in all fatal cases not immediately fatal. It was usually accompanied by hematemesis, abdominal cramps and a marked bloody diarrhea. These gastrointestinal symptoms together with stomatitis, pharyngitis and dysphagia rapidly exhausted the strength of the patient.

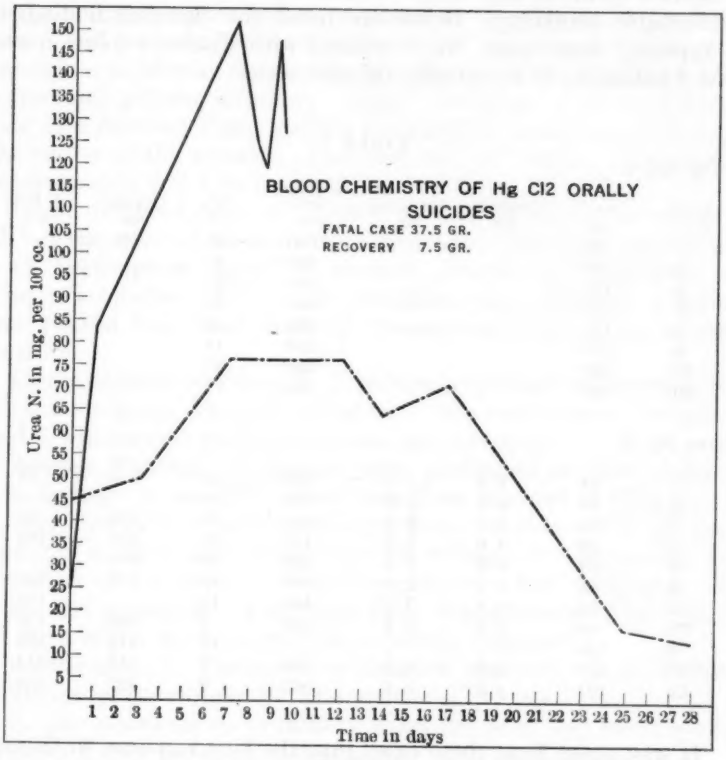
Renal involvement occurred in about one-half of the patients in this series and was diagnosed by findings in the urine or chemical examination of the blood. In this group, polyuria and pollakiuria were not noted, contrary to the findings reported in a much larger series previously treated by the same method.[4] Actual anuria was rare but severe oliguria was noted in several cases. The effect of a chronic nephritis upon which was superimposed a mild acute nephrosis is well shown by the findings in one of the patients listed (Graph 1) (Case 10).

Blood chemical findings, ordinarily attributed to retention were noted in many instances before any interference with the secretion of urine was demonstrable. The findings in these cases were typical of the toxemia as noted by other authors.[1,2,4]

The liver may show definite signs of involvement from the onset as was demonstrated in a very early fatality. Enlargement may be noted gradually day by day as the toxemia progresses. In patients

who recovered the gradual recession of the hepatic enlargement could easily be demonstrated.

There were no definite signs of nervous involvement nor was any pathology demonstrable with reference to the skin, bones, joints or muscles in this group of cases.



GRAPH I.

Laboratory Findings. Striking among the laboratory findings was an early progressive leukocytosis. Patients who recovered from the disease showed a rapid drop to normal in the white-cell count during the period of convalescence. A marked anemia occurred in all severe cases. This was probably not due to hemorrhage alone. The drop in hemoglobin paralleled the decrease in the erythrocytes. There were no evidences of blood regeneration during the acute toxemia. With the color index and volume index of one or less, the whole picture seemed to be a secondary aplastic anemia.

A marked rise in the urea nitrogen, uric acid, creatinin and other nonprotein nitrogenous elements occurred during the intoxication, dropping to normal in a few days if the patient recovered. The alkali

reserve was markedly and characteristically lowered and chlorids were decreased, both describing inverse curves as compared with the urea nitrogen. The effect of therapy in this group was chiefly shown on the chlorids.

A comparison of the blood-chemical findings in cases treated with Fischer's solution and those treated by other methods show a remarkable similarity. Below are listed the chemical findings in 2 typically fatal cases, No. 1 treated with Fischer's solution and No. 2 belonging to an entirely different series:

TABLE I.

CASE No. 1.

Time, days.	Urea N, mg.	Creatinin, mg.	Uric acid, mg.	Chlorids NaCl, mg.	CO_2 vol.	Glucose, mg.	N.P.N. mg.
1	23	...	...	580	48	122	
2	83	...	...	400	45		
5	115	...	...	240	33		
8	150	...	...	600	16		
9	123	...	...	580	16		
9	118	...	...	590	19		
10	146	...	...	580	42		
10	126	...	...	550	77		

CASE No. 2.

1	14	1.5	1.0	500	54	125	33
2	24	2.3	2.0	450	35		—
3	50	2.7	6.3	390	22	108	92
4	78	4.6	6.8	410	20	118	193
5	93	4.6	6.8	490	16	189	—
6	88	4.7	7.0	540	12	109	110
7	95	4.8	7.5	480	13	...	150
8	98	5.6	8.4	430	9	100	150
9	126	...	...	...	13	111	162
10	137	5.0	8.8	450	7	143	214
12	191	5.6	8.4	860	9	122	254

It was noted from these cases that the best response to therapy was shown on the chlorid content, although when alkaline therapy was strenuously used a late sudden rise was noted in the CO_2 content. The changes in neither of these two constituents were clinically accompanied by any marked improvement in the condition of the patient. The types of treatment utilized in both of these cases did not influence to any marked degree the nitrogenous elements, as may be seen by comparing the findings above with those listed in the protocols of the experimental animals poisoned with bichlorid but subjected to no treatment.[1]

A marked decrease in the clotting time and bleeding time was observed during the acute toxemia with return to normal as the patient's condition improved. This perhaps explains why more patients do not die from secondary hemorrhage incident to the marked erosion of the entire gastroenteric mucosa.

Albuminuria, cylindruria and hematuria were noted in about one-half of the cases.

Blood in the stool was observed in 6 cases.

Treatment. For the purpose of this study as few changes as possible were instituted, the attempt being made to adhere closely to the treatment as outlined by Weiss.[4, 5, 6, 7, 8] Nevertheless a few slight changes crept in and are recorded on the charts. In the fatal group all patients received intravenous injections of Fischer's solution and alkalies by mouth, as well as colonic irrigations and saline and glucose infusions. Slight deviations were as follows: One case received 2 gm. sodium thiosulphate intravenously late in the course of the toxemia. One case received sodium bicarbonate intravenously and 1 had a renal decapsulation.

Of the nonfatal cases on Chart I, all had alkalies by mouth and all but one received the active treatment also. One case was treated with thiosulphate alone, 9 received intravenous injections of Fischer's solution while in the remaining cases Fischer's solution was pushed but small doses of thiosulphate were given in conjunction.

Of the patients on Chart II, 13 received expectant treatment only. Five were given Fischer's solution, 1 received glucose infusions and 1 was treated solely by glucose intravenously.

Autopsy Findings. Autopsies were performed on four women. The findings do not differ much from those reported in other cases. A very noticeable involvement of the liver was observed in all cases and in 1 instance this change occurred within three hours after the ingestion of the poison. A diffuse grayish-yellow color gave the brain the appearance of an early fatty degeneration. The vessels of the cerebral hemispheres were intensely congested.

Conclusions. 1. The history of bichlorid ingestion was insufficient evidence for the assumption of a mercurial toxemia.

2. The prognosis as to fatality when the drug was taken orally depended upon the emesis interval.

3. A persistent high leukocyte count, steady increase in the urea nitrogen, marked lowering of the chlorids and a continued decrease in the alkali reserve were unfavorable prognostic signs.

4. A secondary aplastic anemia was noted during the acute toxemia. This was associated with a marked decrease in the clotting and bleeding time.

5. Admission with a temperature of 100° F. or over or with a very low blood pressure was unfavorable but not hopeless.

6. The relationship of dose to fatality or to organic involvement could not be demonstrated.

7. The intravenous use of Fischer's solution did not prevent death from acute mercurialism.

8. The therapeutic value of intravenous glucose and of alkalies by mouth could not be demonstrated.

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RAYNAUD'S DISEASE ASSOCIATED WITH CANCER OF THE STOMACH.

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and
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The following case appears worthy of record on account of the rarity of some of its features, and the light it throws on certain aspects of the pathogeny of Raynaud's disease.

Case Report. A man, aged sixty years, gave no family history of interest, and had had no serious illness during his life until the present trouble. As a child, he had suffered from chilblains, but had had none during the past twenty-five years. He had always felt the cold in his hands in winter, and for as long as he could remember they had tended to become numb after washing in cold water, but these symptoms had never evoked comment. In April, 1927, he began to experience pain in his fingers, and this had steadily become worse, until we saw him on July 12, 1927. The color of the fingers was slaty blue, quite typical of Raynaud's disease. The skin was tense. There were sore cracks round the sides of the nails. The left hand was a little worse than the right. The pain in the fingers was continuous, but increased in paroxysms. At these times the fingers felt as if they were bursting. He also complained of what he called rheumatic pains in the forearms; but these were evidently secondary to the pain in the fingers, because the latter pain sometimes shot half way up the forearm, especially on moving the fingers, and between the attacks pressure on the forearm caused pain in the fingers. He was very apprehensive about the occurrence of pain and at times excitable. There was a coarse reticulated mottling of the skin of both forearms, white areas being surrounded by red streaks. There was a little of the same mottling on the body. There was no impairment to light touch or pin prick. The urine did not contain albumin or sugar. No other physical signs of importance were observed. There was no dyspepsia. The patient was given thyroid by mouth and also treated with copious draughts of fluid before breakfast, according to a modified Einhorn technique. On two occasions an oxygen bath was tried. Dr. Frank Howitt kindly treated him with surging faradism to improve his circulation. He had seven treatments between July 13 and 29. For a short time the condition remained stationary, but he complained of severe pain during the drying of the fingers after the immersion in the water necessary for the treatment. The disease then began to involve one of the thumbs. Consequently he was transferred to the Middlesex

FIG. 1.—Photograph of patient's hand prior to operation.

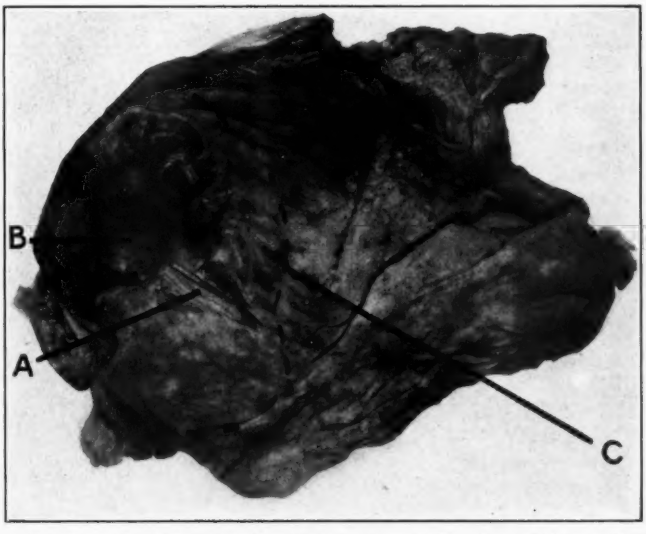

FIG. 2.—Photograph of stomach showing tumor. *A*, Site from which sections were cut; *B*, portion of growth excavated by ulceration; *C*, main boundary of tumor.

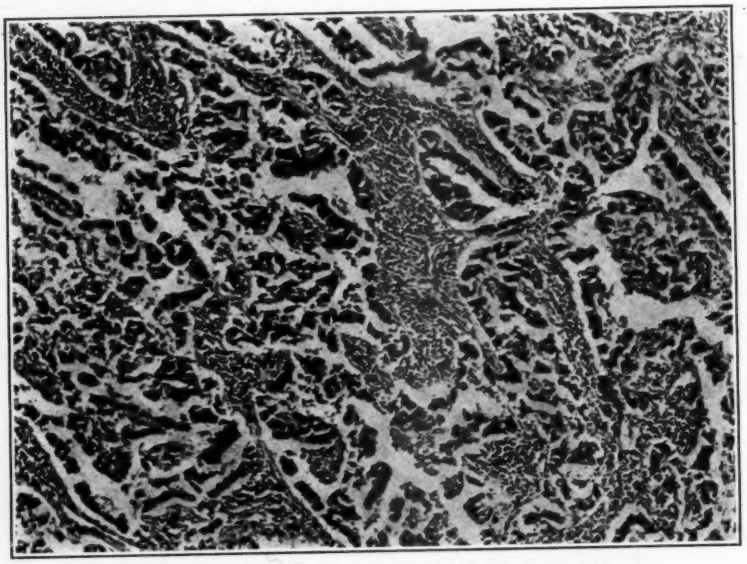

FIG. 3.—Microphotograph of section through stomach-tumor.

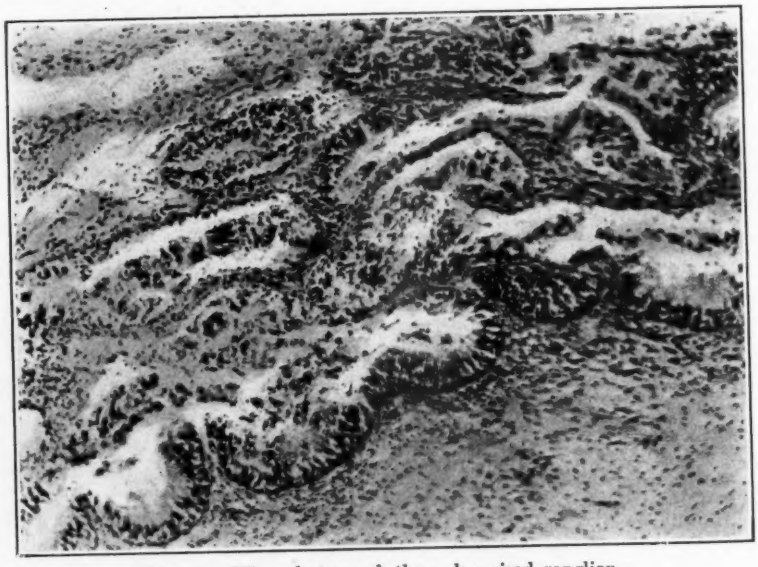

FIG. 4.—Microphotograph through excised ganglion.

Hospital for treatment by intravenous injections of radium emanation, as advocated by Dr. Tominek, or for operation if this failed. While the arrangements for his admission were being made the patient rapidly became worse. His son-in-law stated that during the week prior to admission the pain had been so severe that the patient's groans could be heard in the street outside. It had become necessary to give him morphin several times daily on this account. When admitted to Middlesex Hospital, on August 2, the patient was in a somewhat peculiar mental state due to the pain and the large doses of morphin which he had received. He was resentful of examination, and cried out with pain if anyone approached him. The pain tended to be paroxysmal in character, and morphin in ¼-gr. doses had to be given once or twice daily. Both hands were of a gray-blue color, changing to black at the tip of every finger. They were very tender to the touch, but exhibited no loss of sensation to heat or cold. Sensitiveness to light touch and pain was somewhat increased, the radial pulses were easily palpable, the blood pressure was 145 systolic in both arms. The legs were somewhat cyanosed, but there was no tenderness nor anything suggestive of local asphyxia or gangrene. Both dorsalis pedis arteries could be felt pulsating. There was no abnormality of the heart, a faint systolic murmur in the pulmonary area being the only adventitious sound. Repeated examination of the urine failed to disclose any abnormality. The Wassermann reaction was negative.

The patient's pain was so distressing that it was decided with his approval to secure surgical treatment. On August 9 Mr. Gordon Taylor removed the right inferior cervical sympathetic ganglion. The operation was performed rapidly and without difficulty. The surgeon was proceeding to perform periarterial sympathectomy of the left radial and ulnar arteries, when the patient stopped breathing and failed to recover, in spite of stimulants and cardiac massage.

Intratracheal ether was used throughout the operation, and though the patient's general condition was bad prior to the anesthetic, the collapse appeared to be quite sudden.

Postmortem Findings. The postmortem was unavoidably delayed for several days, and it was impossible to obtain as full an examination as was desirable. The heart was enlarged (11 ounces) and its muscle pale and flabby. The coronary arteries were somewhat atheromatous but patent. There was atheroma of the aorta. The lungs appeared normal. The stomach exhibited a large neoplasm of its lesser curvature, about 1 inch below the esophageal opening. Its diameter was about 4 inches, and it was adherent posteriorly to the pancreas. There were a few metastatic lymph nodes spreading down the abdominal aorta, but no metastases were found above the diaphragm. All other organs appeared normal. No evidence of arterial thrombosis was discovered, but the search for such a possibility was limited.

The inferior cervical ganglion removed at operation was examined microscopically and was found to contain in addition to nervous elements, carcinomatous cells of gastric origin. These arose chiefly from a small gland which was adherent to the ganglion and so removed with it.

Comment. The striking results obtained by Leriche (1913) in relieving the symptoms of Raynaud's disease by periarterial sympathectomy suggested that sympathetic stimulation was the direct cause of the symptoms. Confirmatory evidence has been produced by Adson and Brown, who advantageously removed part of the lumbar sympathetic in a case of Raynaud's disease, and by Davis and Kanavel, who removed the cervical ganglia which supply the upper limbs. In ordinary cases this stimulation is thought to be

due to circulating toxins from the intestines, because Einhorn showed that irrigating the gut with a warm sterile isotonic saline solution through a duodenal tube causes a temporary disappearance of symptoms. Further, it may be mentioned that, many cases of constipation suffer from cold hands.

However, in the present case there was no evidence of any underlying alimentary cause. It is true that no Roentgen ray examination of the alimentary tract was carried out, but the patient stated that his bowels were well opened every day, and the modified Einhorn treatment produced no favorable results. The presence of malignant cells and consequent pressure on the ganglion were quite enough to account for stimulation of the sympathetic ganglion.

Examination of the literature dealing with Raynaud's disease reveals that cases in which this has been associated with other diseases are comparatively rare. Syphilis and malaria, providing the source of bacterial toxemia, have been common causes of Raynaud's disease in certain countries. Migraine and various neuroses have been frequently reported, while cases of angina pectoris, such as those reported by Bard and Schott, may reasonably be regarded as simultaneously occurring expressions of vascular disturbance of nervous origin. A case of duodenal ulcer associated with Raynaud's disease has been reported by Buchanan, and one of gastric ulcer by Friedenwald and Love. These cases, it has been suggested, were examples of trophic disturbance. Keen has described this disease as being sometimes due to cervical rib. It is well known that lesions of the spinal cord also produce rather similar symptoms. Schlesinger has described a case of sarcoma of the cord associated with symmetrical gangrene of the toes. A possible explanation of these examples is that the cervical rib may cause a peripheral and tumors of the spinal cord a central stimulation of sympathetic nerve fibers.

One previous case of Raynaud's disease associated with cancer of the stomach is to be found in the literature (Pasteur and Price Jones). The patient was an obvious example of advanced carcinoma ventriculi with a large abdominal tumor and marked anemia. Toward the termination of this disease, he developed symmetrical gangrene of both feet and of the tip of the nose, a condition, according to the authors, "indistinguishable from Raynaud's disease." Autopsy confirmed the diagnosis of carcinoma of the stomach. No mention of metastases in the neck is made by Pasteur and Price Jones, but in view of the case here recorded, it seems possible that such may have been present, for in our example no obviously malignant glands were observed and had the microscopic sections not been made, their presence would doubtless have been overlooked. It is also to be noted, that Hamilton has described a case of Raynaud's disease associated with carcinoma of the esophagus. Further the Raynaud symptoms appeared for the first time after the carcinoma was well developed.

On reviewing the facts in connection with our case, it seems apparent that the history was unusual in that the severe symptoms made their appearance in spring time and increased steadily throughout the summer. Cases of Raynaud's disease arising in the summer are rare. One such example quoted by Samaja was of malarial origin; the author in reporting it quotes Castellino, who, in 1895, collected 316 cases, all of which displayed their most prominent symptoms in the winter. This fact lends additional support to the view that the carcinoma of the stomach in our case was the direct cause of the symmetrical gangrene, through stimulation of the sympathetic ganglia owing to the deposition of metastatic cells in their proximity.

Summary. A case of Raynaud's disease with symmetrical gangrene of the fingers of both hands is reported. Postmortem examination revealed carcinoma of the stomach with secondary carcinoma cells in the inferior cervical ganglion. The presence of these cells in the ganglion were considered to be the cause of the Raynaud's disease.

One case with closely similar clinical features is recorded in the literature.

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SPONTANEOUS NONTUBERCULOUS PNEUMOTHORAX IN INFANCY AND CHILDHOOD.

A Review of the Literature with Three Additional Cases.

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A careful review of the literature from 1844 to the present date reveals the decided rarity of spontaneous pneumothorax of nontuberculous origin in infancy and childhood. For this reason, and also because in the absence of roentgenography a diagnosis might have been missed, I wish to add 3 cases of such a nature to the compilation in the accompanying tables.

Cases.	Author.	Publication.	Age.	Etiology.	Result.
1–20.	Lentz quoted by Cnopg and Tidestrom (see below)	Review of the literature 1844–1880. Original report in Inaugural Dissertation Würzburg; not obtainable	?	Gangrene 11 emphysema 3 apoplexy 3 empyema 1 hem. infarct 1 bronchiectasis 1	?
21.	Huttenbrenner	Jahrb. f. Kinderheilk., 1872, **5**, 206	7 yrs.	Typhoid, pneumonia, pneumothorax containing pus	Died.
22.	"	"	4 yrs.	Pneumonia	Died.
23.	Ruge	Ztschr. f. Geburt. u. Gynec., 1878, **2**, 31	Newborn	Rupture of pleura	Died.
24.	Steffen	Jahrb. f. Kinderheilk. 1883, **19**, 105	2 yrs.	Mediast. emphysema, post-tracheotomy	Died. Died.
25.	Malinoski	Jahrb. f. Kinderheilk., 1888, **22**, 273 (reference)	4 yrs.	Pertussis	Died.
26.	Ast	München. med. Wchnschr., 1892, **39**, 605	4 yrs.	Sharp stone perfor. empyema	Died.
27.	Knopf	München. med. Wchnschr., 1893, **40**, 123	2 yrs.	Pertussis	Died.
28.	"	"	2 yrs.	Diphtheria, tracheotomy	Died.
29.	Carr	Transac. Am. Ped. Soc., 1895, **7**, 69	10 yrs.	Pneumonia empyema	Recovered.
30.	Carslow	Glasgow Med. J., 1895, **43**, 274	3 yrs.	Plum stone perforation	Recovered.
31.	Gebrack	These de Paris, 1900–01, p. 44	10 yrs.	Bronchiectasis	Died.
32.	Steffen	Zur Path. Anat. des Kindesalters: Bergmann, 1901, p. 273	1 yr.	Measles, pneumonia	Died.
33.	"	"	5 yrs.	Diph. infarct	Died.
34.	"	"	3 yrs.	Emphysema	Died.
35.	"	"	12 yrs.	Subcut. emphysema after trauma	Recovered.
36.	Zuppinger	Wien. klin. Wchnschr., 1902, **15**, 13	3 yrs.	Corn kernel perforating lung	Died.
37.	Bovaird	Arch. Pediat., 1903, **20**, 825	3 yrs.	Measles, pneumonia	Died.
38.	"	"	5 yrs.	Pneumonia	Recovered.
39.	"	"	3 yrs.	Measles, pneumonia	Died.
40.	"	"	6 mos.	Pneumonia	Died.
41.	"	"	4 yrs.	Abscess of lung	Died.
42.	Hall	Med. Record, 1906 **69**, 296	10 yrs.	Pneumonia	Died.
43.	Meyer	Monat. f. Kinderheilk., 1916, **14**, 209	9 mos.	Influenzal abscess of lung; pneumothorax with pus	Died.
44.	"	"	5 mos.	Influenzal bronchitis	Recovered.
45.	Sior	Jahrb. f. Kinderheilk., 1921, **94**, 130	11 yrs.	Emphysema (bilateral pneumothorax)	Recovered.

Cases.	Author.	Publication.	Age.	Etiology.	Result.
46.	Schoenfeldt	Monat. f. Kinderheilk., 1922, **24**, 226	4 yrs.	Pneumonia (abscess)	Died.
47.	"	"	15 mos.	Pneumonia (abscess)	Died.
48.	"	"	18 mos.	Grippe (emphys. bleb)	Died.
49.	"	"	10 mos.	Emphysema ?	Died.
50.	Kohler	Klin. Wchnschr., 1923, **2**, 2133	8 yrs.	Tear of lung (pneumothorax with pus)	Died.
51.	Schaltema	Nederl. Maanschaft vor Verlosk, 1917, **6**, 6	7 wks.	Probably congenital defect	Recovered.
52.	Vera	Arch. Esp. de Pediat., 1923, **7**, 358	12 yrs.	Pneumonia, empyema	Died.
53.	"	"	3 yrs.	Pneumonia, cardiac	Died.
54.	"	"	3 yrs.	Typhoid	Recovered.
55.	Pehu, Barre, et Reboul	Soc. Med. des Hopitaux, 1923, **7**, 23	11 mos.	Pneumonia, empyema	Died.
56.	Ross	Med. Clin. No. America, 1924, **7**, 1941	2 yrs.	Pneumonia, empyema	Recovered.
57.	St. Engel	Pfaungler and Schlossman Vogel, 1924, **3**, 658	1 mo.	Congenital ?	Died.
58.	Ernberg	Hygeia, 1925, **87**, 4	7 wks.	Lung abscess	Recovered.
59.	Tidestrom	Acta Pediatrica, 1925, **4**, 380	3 mos.	Cong. bronchiect. or emphysema	Recovered.
60-64	Dove	Revue de Chirurgie, 1925, **63**, 8	5 cases 1 to 15 yrs.	Hydatid	?
65.	Moncrieff	Brit. J. Child. Dis. 1926, **27**, 43	1 yr. 10 mos.	Emphysema bleb	Recovered.
66.	Benjamin	Arch. f. Kinderheilk., 1926, **77**, 241	10 yrs.	Pertussis	Recovered.
67.	"	"	9 mos.	Pertussis	Recovered.
68.	"	"	2 yrs.	Pneumonia	Recovered.
69.	"	"	18 mos.	Bronchiectasis	Recovered.
70.	"	"	5 yrs.	?	Recovered.
71.	Rodgers	Arch. Pediat., 1927, **44**, 447	8 yrs.	Pneumonia, empyema	Recovered.
72.	Johnson	Am. J. Dis. Child., 1927, **33**, 740	2 yrs.	Pneumonia	Recovered.
73.	"	"	1 mo.	Rupture subpleural abscess, pyopneumothorax	Died.
74.	"	"	10 wks.	"	Died.
75.	"	"	3 yrs.	"	Died.
76.	"	"	1 mo.	"	Died.
77.	"	"	2 yrs.	"	Died.
78.	"	"	17 mos.	"	Died.
79.	"	"	17 mos.	"	Recovered.
80.	"	"	8 mos.	"	Died.
81.	"	"	6 mos.	"	Recovered.
82.	Author		11 mos.	Pneumonia	Recovered.
83.	"		16 mos.	Pneumonia	Recovered.
84.	"		18 mos.	Pneumonia	Recovered.

Etiology and Pathogenesis. By spontaneous pneumothorax is meant the presence within the pleural cavity of air which gets there without introduction by artificial means. Excluded, therefore, are such instances of pneumothorax as arise after exploratory puncture of Potain, or after therapeutic use of air, or after trauma which allows a continuity of the external atmosphere with the pleural cavity.

Tuberculous disease of the lungs and pleuræ is a frequent cause of spontaneous pneumothorax; in adults it is estimated as being the etiologic factor in 90 per cent or more of the cases, in children it is considered as causing about 40 per cent of them.[1, 2, 3] The pneumothorax then arises from superficially located fresh cavities which rupture into the pleural space. It may also occur in older processes when adhesions or fibrosis are not complete.

The relative frequency of the different types of nontuberculous etiology, as represented on the basis of the 84 cases compiled follows: pneumonia, 30 (35.7 per cent) of these 3 are associated with measles, and 1 with typhoid; gangrene, 11 (13 per cent); emphysema 11 (13 per cent); of these 2 are posttracheotomy, 1 after trauma, 1 after grippe (experimental evidence of pneumothorax following mediastinal emphysema in connection with tracheotomy is offered by Champneys;[4] hydatid, 5 (5.9 per cent); pertussis, 4 (4.7 per cent); congenital defect ? 4 (4.7 per cent); lung abscess, 3 (3.5 per cent); bronchiectasis, 3 (3.5 per cent); foreign body, 3 (3.5 per cent; 1 a sharp stone, another a plum stone, the third a corn kernel which by perforating the bronchus, lung tissue and pleura gave rise to pneumothorax; lung apoplexy, 3 (3.5 per cent); empyema 1 (1.1 per cent), where the lung and bronchus are invaded by the exudate. Infarction (diphtheria), 1, and (hemorrhage), 1, and 1 each of typhoid, influenzal bronchitis, rupture of pleura and tear of the lung.

Expressed in terms of pathogenesis, pneumothorax may be caused by rupture (*a*) following degeneration or (*b*) due to congenital or mechanical defect of the lung. The degeneration may be abscess formation, gangrene, bronchiectasis, infarction (diphtheria or typhoid), empyema breaking into the lung, or apoplexy. The rupture may be secondary to a congenital defect (aplasia? or emphysema? or bronchiectasis?), or to emphysema (already existent or following tracheotomy, or pertussis), or to foreign body (perforation of bronchus, and lung and pleura).

The pneumothorax which arises may be simple or complicated with the presence of an exudate. It may be transient or prolonged, depending upon the etiology, the extent, the complications, and whether the pneumothorax is open, closed, or of the check-valve variety. In an open one, the point of entrance which remains patent permits an easy to-and-fro movement of the air. When, however, there is an immediate closure of the opening the pneumothorax is designated closed and the air in such may be quickly absorbed.

FIG. 1.—E. G. Pneumonia at the right base in the region of the cardiophrenic angle and root of the lung.

FIG. 2.—E. G., February 12, 1927. Ten days later. Simple partial multilocular pneumothorax occupying the site of the pneumonic infiltration now in resolution.

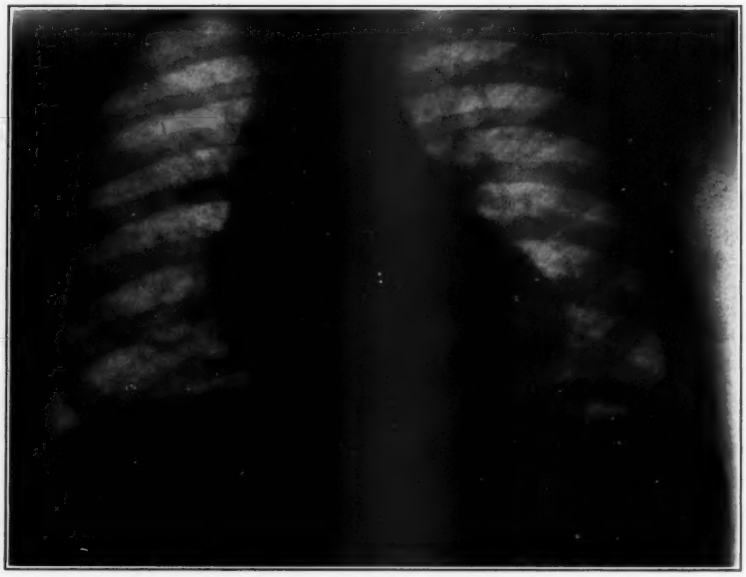

FIG. 3.—E. G., May 23, 1927. There is now no evidence of the previous pneumona or pneumothorax.

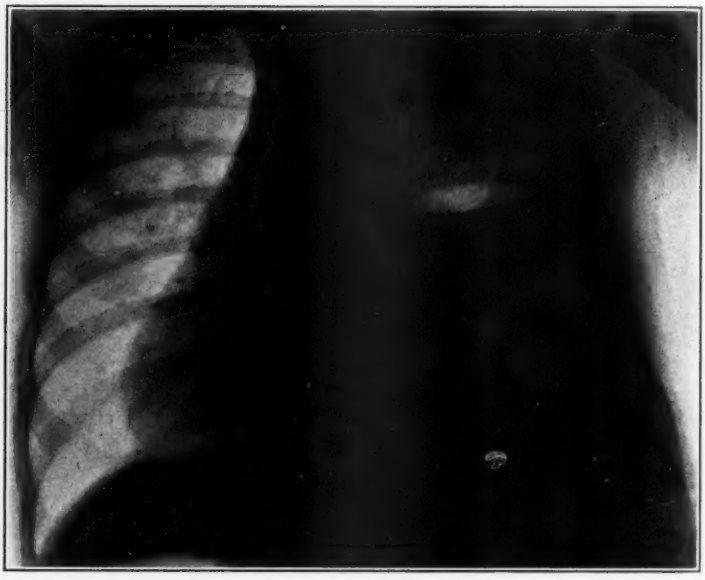

FIG. 4.—R. L., May 13, 1928. Pneumonia and pneumothorax of the multicular variety apparently simple, occupying the right lower lobe.

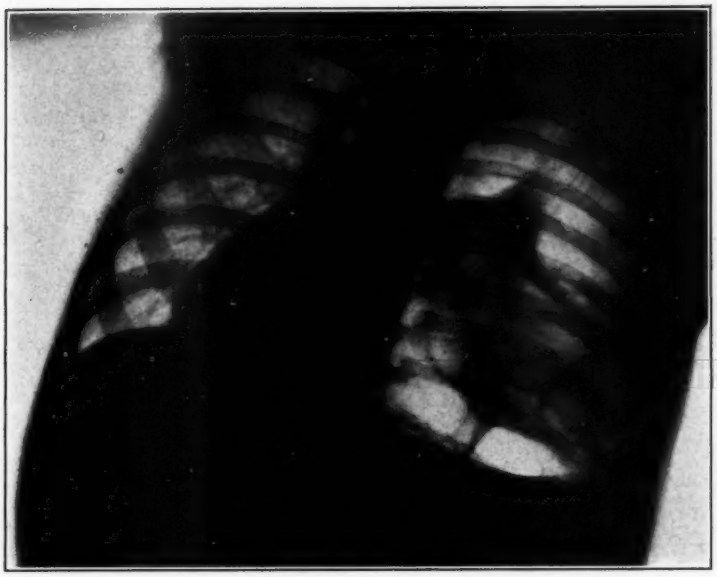

FIG. 5.—R. L., June 7, 1927. Multilocular total pneumothorax of the right side with displacement of the mediastinum toward the opposite side and depression of the diaphragm of the same side.

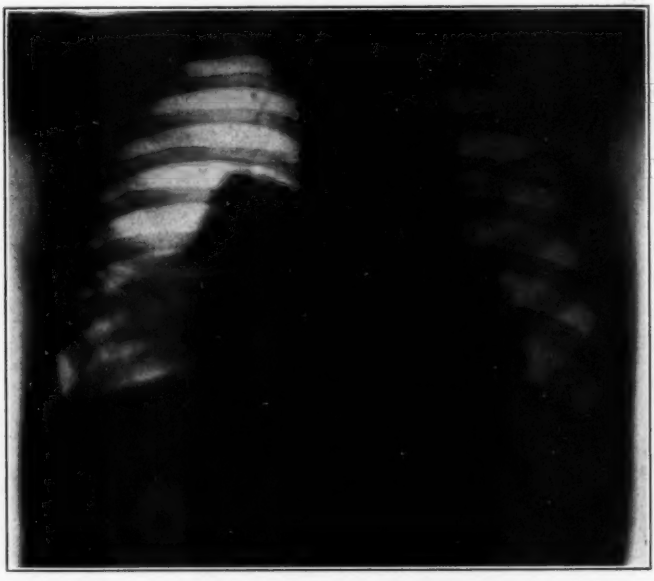

FIG. 6.—R. L., June 10, 1927. The pneumothorax has expanded to become almost unilocular. The compressed lung is seen as a shadow at the root of the lung.

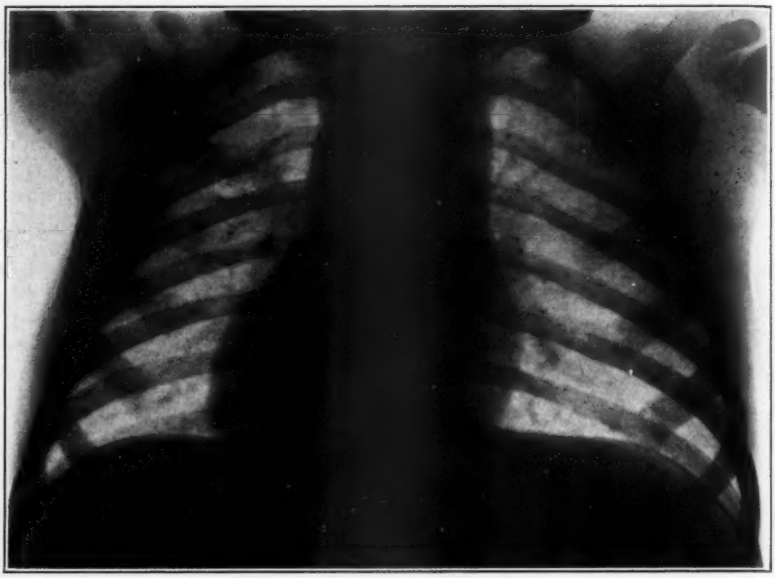

FIG. 7.—R. L., August 23, 1927. There is complete restoration of the lung to normal.

FIG. 8.—W. S., May 13, 1927. Simple partial unilocular pneumothorax with a pneumonic infiltration surrounding it, in the left upper lobe.

FIG. 9.—W. S., May 17, 1927. Pneumonia undergoing resolution, unilocular pneumothorax still present.

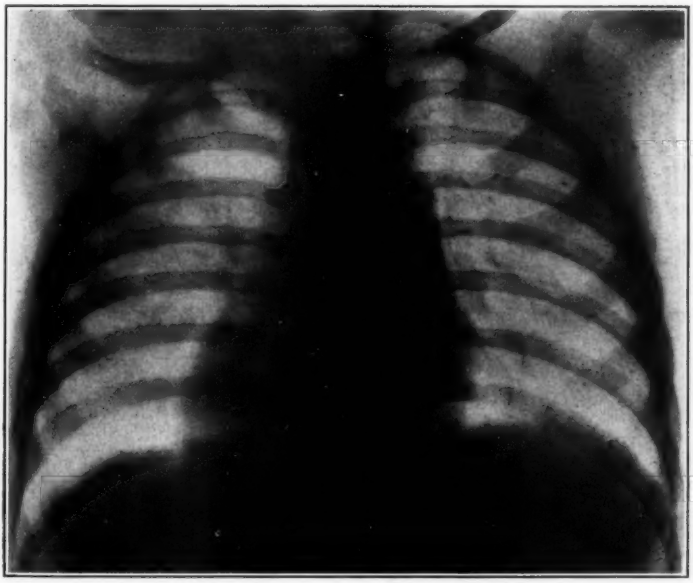

FIG. 10.—W. S., August 4, 1927. Complete restoration of the lung to normal.

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At times fibrin or a flap of tissue acts as a valve (check-valve) which allows the ingress of air but not the egress, so that here as in the closed type also, if the enclosed air is large in amount and the tension, therefore, augmented, there may result a displacement of the mediastinum toward the unaffected side and a depression of the diaphragm on the same side. Pneumothorax may be unilateral or bilateral, partial or total, unilocular or multilocular, as well as simple or complicated.

Case Reports. CASE I.—E. G., aged sixteen months, was admitted to the pediatric service of the Mount Sinai Hospital February 1, 1927, and discharged March 25, 1927. The chief complaint on admission was fever, swellings of the lower extremities for three weeks and cough of one week's duration. The family, developmental, and past infectious history was essentially negative. The present history began three weeks before admission with fever of sudden onset. A few days later a swelling, red, hot and tender, was first observed on the right thigh. The following day another was noticed on the right hand and one on the right heel. The temperature ranged between 101° and 105° F. The swellings were incised and according to the mother she was told that the child had "pus in the blood." The fever has continued and an increasing pallor has been noticed. Five days ago breathing became noisy and labored.

On examination, the child appeared acutely ill. The cheeks were flushed, the respirations accelerated and shallow. There were healing incisions on the right thigh, the right hand, and the right heel. The right lung revealed abnormal signs: at the base posteriorly there were dullness, bronchial breathing, no râles. A diagnosis was made of general bacteriemia with localizing manifestations in the extremities, as abscesses, and in the lung as a pneumonia. The roentgenogram on admission showed a pneumonia of the right base in its mesial portion at the root of the lung. A transfusion was administered the next day. The right base now had râles as well as dullness and bronchial breathing. Two days later transfusion was repeated. The lung signs remained unchanged. Blood cultures were now reported as positive for Streptococcus hemolyticus (beta). The roentgenogram of March 9 showed a multilocular partial pneumothorax at the right base in the area of the pneumonic infiltration. The fever continued until March 13. The blood culture was reported negative for the first time on March 18. The dullness persisted and the bronchial breathing too; no râles were heard except on March 24. On that day, clubbing of the fingers was first noticed. The general condition steadily improved and the patient was discharged six weeks after admission. Follow-up of the case revealed a clearing of the process; a roentgenogram made on May 25, 1927, failed to show any abnormality. There are no residue in the lungs and the child is doing well.

CASE II.—R. L., aged eleven months and three weeks, was admitted May 13, 1927, discharged July 4, 1927. The chief complaint was fever and cough of one week's duration. The family history was essentially negative. Except for frequent sore throats accompanied by fever, each attack lasting a few days, the past history was negative. The present illness began one week ago with fever of 104° F. and cough. She was taken to the dispensary where a diagnosis was made of tonsillitis, bilateral otitis media and grippe. A left meringotomy was done the following day. No improvement occurred and after three additional days of fever she was brought to the hospital.

On examination, the patient appeared acutely ill, cyanotic, dyspneic and

coughed frequently. The right side of the thorax seemed immobile. Over the right base anteriorly and posteriorly there were dullness, diminished breath sounds, and scattered râles. The upper lobe had an impaired note and a few scattered râles. The temperature of 104° F. persisted for four days and then fell to normal. The roentgenogram on admission showed a pneumonia of the right lower lobe and middle lobe with an area of pneumothorax (localized and multilocular) in the region of the cardiophrenic angle. For the first six days in the hospital (until May 19), there persisted a marked dullness and diminution of breath sounds over the right base. A roentgenogram on May 19 showed a resolution of the pneumonia but an extension of the pneumothorax so that it occupied the lower three-fourths of the right lung field. After this. and until discharge on July 4, there remained dullness and distant bronchial breathing at the right base. On June 2 the roentgenogram showed a complete pneumothorax of the right side, multilocular, with compression of the lung toward its root, displacement of the mediastinum toward the opposite side, and depression of the diaphragm on the same side. One month later a Roentgen ray examination showed complete restoration to normal. Since then it has remained so.

CASE III.—W. S., aged eighteen months, was admitted May 13, 1927, discharged May 22, 1927. The chief complaint was cough and fever of three weeks' duration. Family and previous history were essentially negative. The present history is said to have begun with bronchitis which persisted for a few months. For the last two weeks preceding admission, there was fever (height not known), listlessness and cough.

On admission, the child did not appear very ill. Save for the lung signs there were no other abnormalities noted. In the first and second interspaces anteriorly, there was dullness and distant bronchial breathing; posteriorly down to the level of the angle of the scapula there was also dullness and distant bronchial breathing. The upper part of the axilla also had the same signs. On the basis of the physical signs and the general appearance of the patient a provisional diagnosis of unresolved pneumonia was made. The roentgenogram at that time showed a resolving pneumonia of the left upper lobe containing in its lowermost part a unilocular pneumothorax, oval in shape, about the size of an olive. After the second day of residence in the hospital, the temperature became normal and remained so. Four days after the initial roentgenogram another showed an almost complete resolution of the pneumonic infiltration except for a narrow ring immediately surrounding the single loculus of pneumothorax which occupied the lateral two-thirds of the first and second interspaces anteriorly. The dullness persisted and the breath sounds were faintly bronchial. The pneumothorax appeared to have grown larger a month later but by August 23, 1927, there were no evidences of its presence in the roentgenograms. Since then, there have been no residua clinically or roentgenologically.

Roentgen Diagnosis. The roentgenogram is usually so characteristic as to make the diagnosis unequivocal. Pneumothorax is seen as partial or total, unilocular or multilocular. When unilocular, there is an area of varying size which contains no lung markings and which is sharply circumscribed from the lung tissue by a linear shadow (Case III, W. S.). The multilocular variety has a weblike or fish-net appearance there being sharp definition of each loculus the size of which varies (Cases I and III). At first multilocular, a pneumothorax may become unilocular with increasing tension of the contained air (Case II). Occasionally, as in Case III, W. S., when a

single loculus occurs in the presence of an infiltration, the area may be delimited by a thick outline which is suggestive of a cavity. In childhood, the interpretation of the tuberculin reaction as well as the clinical course is of invaluable aid in the diagnosis. A total pneumothorax under increased tension as in the check-valve or closed varieties will compress the lung toward its root where, because of its airlessness, it is seen as a dense shadow. The mediastinum, too, will suffer displacement toward the uninvolved side and the diaphragm of the same side is depressed. If fluid be present, its horizontal level will be visualized below the air content when the roentgen exposure is made with the patient in an upright position. During the fluoroscopic examination the patient may be moved into different positions (inclined forward, backward, toward the sides) and at varying rapidity, so that alteration in the level and position of the fluid may be seen. If the pneumothorax is total, a pendulous movement of the mediastinum is seen on active respiration. At times, too, the diaphragm of the affected side may show a paradoxical ascent and descent.

Comment. The total number of cases I have been able to compile from the literature is 84. Of this group, 25 have lacked adequate information as to age and result so that they could not be used in obtaining some of my percentages. Of the 59 remaining, 17 (28 per cent) were in infants below one year of age. Nineteen (32 per cent) were complicated by an empyema. There were 34 deaths, (57 per cent mortality).

The 3 cases I have added all occurred at the close of pneumonic processes, when clinically there was reason to believe they were going on to resolution. All were repeatedly negative to tuberculin tests. Even after the roentgenograms had revealed the presence of air in the pleural cavity the clinical signs were certainly not suggestive of pneumothorax. In the instance E. G., Case I, and R. L., Case II, there were large enough accumulations of air, indeed, to warrant those signs that are so easily elicited in adults with pneumothorax: coin sound, metallic tinkling, tympany, amphoric breathing. What all my cases did have was persistent dullness and suppressed or distant bronchial breathing. In the absence of the roentgenograms and fluoroscopy I have no doubt that the diagnosis may have been missed. The sparsity of clinical signs commensurate with the pathology is indeed striking. It is noteworthy, too, that autopsy will frequently reveal the presence of pus which has not been recognized either clinically or roentgenologically. One cannot then always separate the simple from the complicated. My cases were, as far as known, simple pneumothorax.

Summary. 1. A review of the literature from 1844 to the present date allows a tabulation of 84 cases of spontaneous pneumothorax of nontuberculous etiology.

2. The etiology and pathogenesis of spontaneous pneumothorax

with particular reference to the accompanying compilation was considered. Tuberculous disease is probably the most frequent single cause. Pneumonia follows with a 35.7 per cent incidence in this tabulation; then emphysema and gangrene. Expressed pathogenetically, pneumothorax may be caused by (*a*) degeneration in the lung (abscess, gangrene, bronchiectasis, infarction, empyema or (*b*) rupture of the lung due to congenital defect, emphysema, foreign body.

3. The roentgen diagnosis is discussed. Pneumothorax, either open, closed, or of the check-valve variety, may be seen as partial or total, unilocular or multilocular, simple or complicated, and unilateral or bilateral.

4. Three cases of nontuberculous spontaneous pneumothorax are added to the literature: all were postpneumonic, simple (uncomplicated), and made uneventful recoveries. Their recognition was made on the basis of roentgenography; they were characterized by a sparsity of clinical manifestations and signs which probably would not have sufficed to enable the diagnosis in the absence of the roentgenograms and fluoroscopy.

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THE CLINICAL SIGNIFICANCE OF THE LIFE CYCLE OF THE PARASITE IN INDUCED MALARIA.

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and
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The malarial treatment of general paralysis introduced by Wagner von Jauregg, has achieved universal recognition. This form of therapy has been used with conspicuous success in the United States; Bunker and Kirby[1] of the Psychiatric Institute, having been among the very first to publish significant results in this country. Our strain of malaria has been artificially transmitted by intravenous inoculation from patient to patient since June, 1923.

Over 300 general paralytics have been so inoculated and the strain appears to retain its "virulence" in inducing malaria.

Within the past two years, we have been impressed by the fact that our strain of malaria does not form fully developed gametocytes (sexual forms) in the peripheral blood of inoculated patients even after ten or more paroxysms. Upon the face of it, this would appear to be an unusual finding for in the natural course of events it might be expected that the malarial parasite would develop sexual forms in the human host as it does in "natural" or mosquito malaria. However, Gerstmann,[2] whose comprehensive review of the literature is authoritative, states that not alone in Wagner von Jauregg's Clinic but also in others, the sexual forms of the malarial parasite were absent in the peripheral blood of general paralytics artificially inoculated with malaria.

The necessity for an intensive study of the life cycle of the parasite in artificial (inoculation) malaria is important from the biologic as well as the practical point of view. To this end, the following procedure was employed. Three women with general paralysis in the Manhattan State Hospital were inoculated intravenously on November 23, 1927, at 3 P.M. with 3 cc. of citrated blood containing numerous malarial parasites. Rectal temperatures were taken every three hours until four paroxysms had occurred. Then the temperature was taken hourly for thirty consecutive hours and blood smears made in duplicate. The latter were stained with the Wright modification of the Romanowsky stain (Burroughs, Wellcome & Co., "Soloid"). For special examinations, the Pappenheim staining method was employed. All slides were examined thoroughly under the oil-immersion objective. The results are shown in Figs. 1, 2 and 3.

It will be noted in Figs. 1 and 2 that the temperature charts are given for the first two paroxysms and for the fifth paroxysm, when hourly temperatures were taken. The break between December 2 and 5 on each of these charts indicates the omission of superflous data. Whenever a blood smear was made, the results of the microscopic examinations are indicated by letters which are explained in the legend of Fig. 1. The predominant forms of the parasite are listed one above the other in order of greatest incidence. Thus, P, over M, over S, indicates that presegmental forms were present in greatest abundance, followed by mature schizonts and segmentals, respectively. As is customary in benign tertian malaria, all forms of the parasite may be found at any time. This holds true for artificial (inoculation) malaria as well as for "natural" or mosquito malaria, as may be seen from our data. In general, young ring forms, or crescents, are few in number at the beginning of a paroxysm but become more numerous after the height of the febrile curve has been reached. The same may be said for the segmentation forms. Mature schizonts and presegmental forms are invariably present.

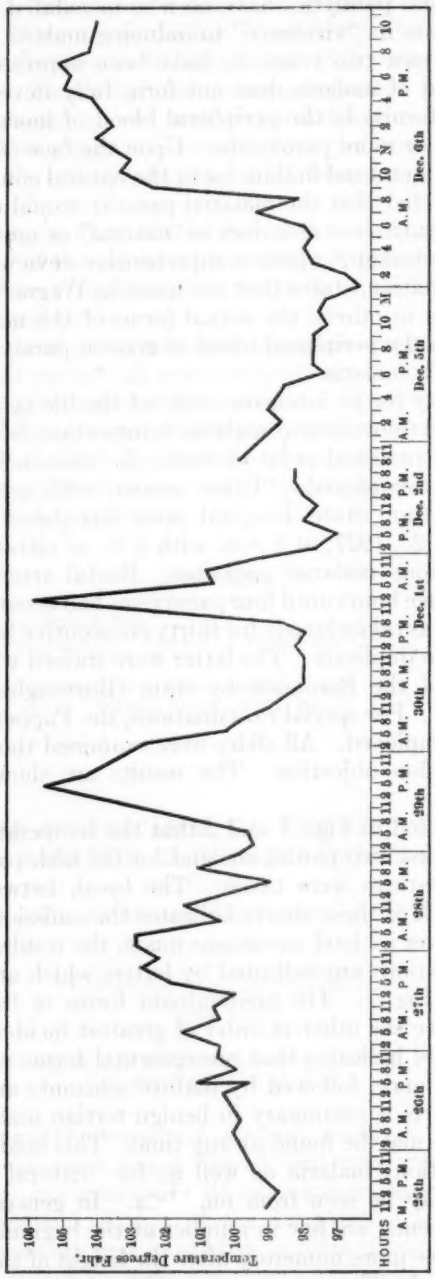

FIG. 1.—A. H. K. Inoculated with malaria November 23, 1927, at 3 P.M. O, no parasites; R, rings; M, mature forms (schizonts); P, presegmentals; S, segmentals.

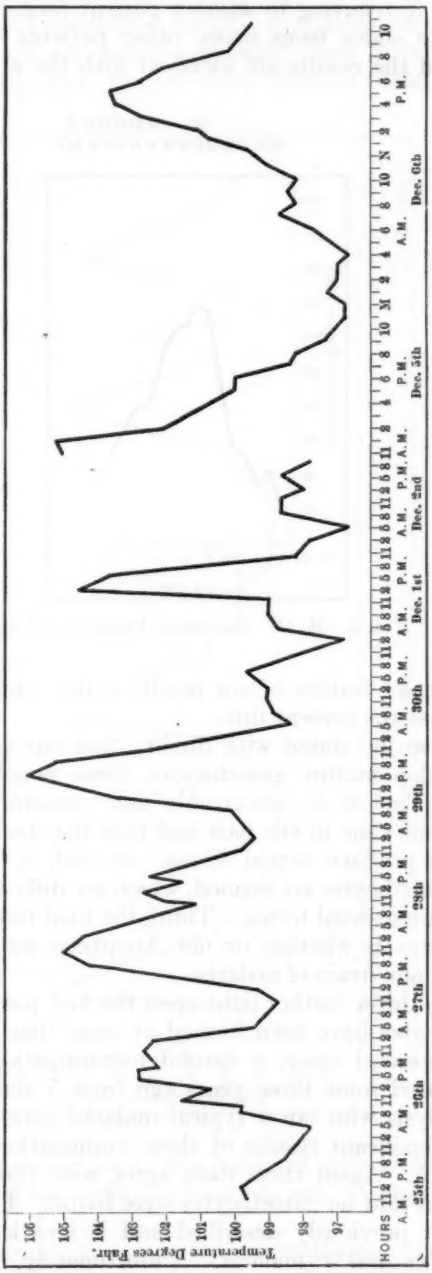

FIG. 2.—M. H. Inoculated November 23, 1927 at 3 P.M.

The data presented in Figs. 1 and 2 have been augmented by those of Fig. 3, referring to another patient (male) recently inoculated. Single slides from many other patients have also been examined and the results are identical with the above.

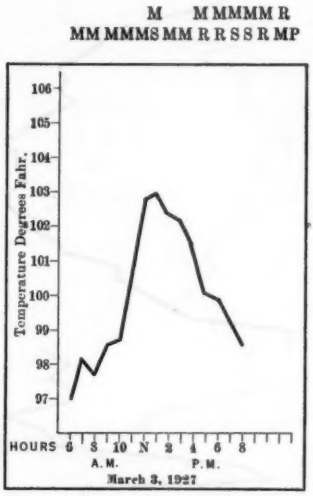

FIG. 3.—K. D. Inoculated February 3, 1927.

The significant feature of our results is the complete absence of gametocytes at the present time.

Before it can be stated with finality that our strain of malaria fails to develop mature gametocytes, three possibilities must be considered. First it is conceivable that gametocytes have been formed at some time in the past and that the strain has since lost its power to produce sexual forms. Second, it is possible that immature gametocytes are formed, which are difficult to distinguish from immature asexual forms. Third, the final test of the presence of sexual forms is whether or not Anopheles mosquitoes can be infected with our strain of malaria.

In order to throw further light upon the first possibility, namely, that gametocytes have been formed at some time in the past but have not appeared since, a careful reëxamination was made of smears prepared some three years ago from 5 male patients with general paralysis who ran a typical malarial course after inoculation. The significant results of these examinations are shown in Figs. 4 and 5. Again these data agree with those presented in Figs. 1 to 3 in that no gametocytes were found. The asexual cycle parallels that previously described and is identical with that of mosquito ("natural") malaria. Unfortunately, there were no smears available for reëxamination from patients treated five years

ago. In all probability gametocytes might have been found in the first few passages of our strain of malaria.

As to the second possibility, namely, that immature gametocytes are formed which are indistinguishable from immature asexual forms, we can only state that we have failed so far to identify any

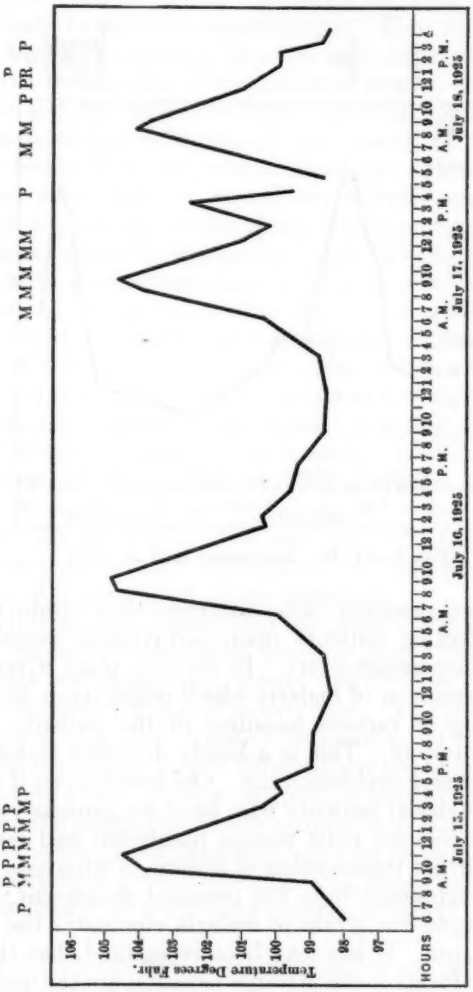

FIG. 4.—H. B. Inoculated July 4, 1925.

gametocytes. Verification at the hands of authorities in this field has been solicited but sufficient time has not yet elapsed for a final opinion.

The third consideration, namely, mosquito infectivity, is to be attempted again this summer. Previous efforts to raise mosquitoes

for this purpose were unsuccessful because of failure to obtain an adequate supply of larvæ. Gerstmann claims that it was impossible to infect mosquitoes with the blood of his patients. Incidentally, it may be mentioned that despite repeated attempts with various media to artificially cultivate the malarial parasite we have as yet been unable to obtain growth for more than a few generations.

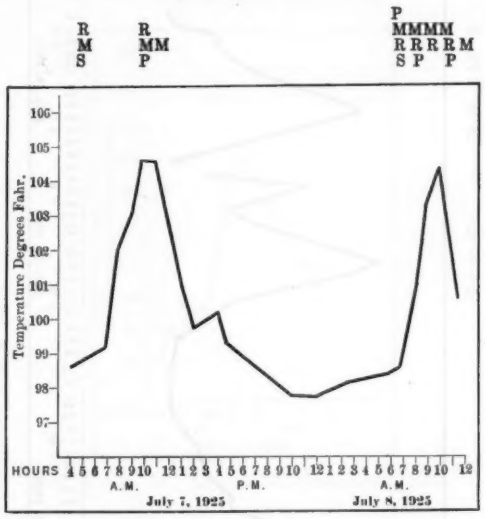

FIG. 5.—T. K. Inoculated June 24, 1925.

An important practical value attaches to a strain of malaria capable of infecting patients upon intravenous inoculation but failing to produce gametocytes. In the first place it removes any danger of transmission of malaria which might occur as a result of faulty screening or careless handling of the patients. In other words, it is fool-proof. This is a highly desirable feature for hospitals where nursing problems exist. Obviously, even if stray Anophelines bite malarial patients who have no gametocytes in their blood, the Anophelines must remain uninfected and consequently all danger of further transmission of malaria is removed.

Even more significant from the practical standpoint, is the fact that a gametocyte-free strain of malaria eliminates the possibility of malarial relapse. It has long been recognized that the gametocytes, of all the forms of the malarial parasite, are the most resistant to quinin. Experience has also demonstrated that induced (inoculation) malaria yields more readily to quinin than does "natural" malaria. Carrying the matter one step further, we have every right to assume that relapses will not occur following adequate quinin dosage in artificial (inoculation) malaria where gametocytes are absent. This has been adequately demonstrated throughout our

series of inoculated patients, where no patient in our series of more than 300 cases has had a malarial relapse.

In this connection, we might mention that upon several occasions we have observed a very interesting phenomenon, namely, that fever of nonmalarial origin which developed shortly after the completion of the malarial course (from one to three days or more) had a tendency to be of the malarial type. Thus in 2 patients who developed bronchopneumonic foci two days after quinin had been given for the termination of the malarial course, the temperature was normal and the blood free from parasites. But the temperature which developed subsequently as a result of the pneumonia was again decidedly paroxysmal in character. However, repeated blood examinations failed to reveal any malarial parasites whatsoever. Upon the administration of wet packs and heart stimulants the pneumonic symptoms disappeared and with them, the temperature. A similar phenomenon was noticed in a tabetic who, three, five and six days respectively after the completion of his malaria, again developed a paroxysmal temperature without having any malarial parasites in his blood. The cause of this new elevation in temperature was found to be a cystitis which healed up under the administration of urotropin. Accordingly, it almost seems as though the center for the regulation of temperature becomes accustomed, during malaria, to a definite course. The tendency to continue this course persists, so to speak and the regulatory center reacts to infections of nonmalarial origin in the same way. So far we have been unable to find any clearer explanation for this phenomenon nor have we found it mentioned in the literature.

The conclusion to be drawn from our studies is that our strain of malaria is apparently free from gametocytes. This means, biologically, that our strain has become "sterile;" in other words, it has lost its capacity for sexual propagation. The absence of gametocytes makes it impossible to infect mosquitoes. Therefore, instead of having the customary double life-cycle our strain has only a single life-cycle in man alone. Such an adaptation has obvious advantages. It eliminates the possibility of the transmission of malaria to other members of the community and precludes the occurrence of malarial relapse. Aside from purely scientific considerations, therefore, our strain of malaria is of indubitable practical value.

Summary. 1. More than 300 patients with general paralysis have been inoculated intravenously with a single strain of malaria which has been therapeutically effective.

2. A detailed microscopic study of the life-cycle of this parasite has been made by examining blood smears taken hourly from 4 patients at the present time and from 3 patients inoculated with malaria about three years ago.

3. The significant finding was the total absence of gametocytes

(the sexual forms of the malarial parasite). The asexual cycle of this strain of malaria is identical with the asexual cycle of "natural" (mosquito) malaria.

4. A malarial strain free from gametocytes is of considerable practical value in the treatment of general paralysis in that: (*a*) it eliminates the possibility of the transmission of malaria to other members of the community; (*b*) it precludes the occurrence of malarial relapse following adequate quinin administration.

NOTE.—It is a privilege to acknowledge our indebtedness to Dr. G. H. Kirby, Director of the Psychiatric Institute, for his interest and counsel throughout this study and to thank Mr. Sidney B. Meyers for his technical assistance.

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ACCESSORY SPLEENS—THEIR SIGNIFICANCE IN ESSENTIAL THROMBOCYTOPENIC PURPURA HEMORRHAGICA.*

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IN 1731 Werlhof laid the foundation of our present conception of the disease "purpura hemorrhagica" as a distinct entity; Hayem, the French hematologist, discovered the thrombocytes (platelets). Denys was the first to have observed the paucity of platelets in this condition in a case observed by him; Wright established the fact that the megakaryocytes were the parents of the platelets; increased clot retraction time in this disease was brought out by Hayem. This was demonstrated by Pagniez to be due to diminished platelets. Hayem and independently Duke called attention to the increased bleeding time so characteristic of this condition; Hess evolved the capillary resistance or tourniquet test which is commonly used in the diagnosis of purpura hemorrhagica.

* Since revising the proof of our paper on "Accessory Spleens," our attention has been called to Finklestein's statement in the "Jahreskurse für Ärztliche Fortbildung," June, 1921, 12 Jahrgang, page 13, that Accessory Spleens may be responsible for recurrence of symptoms after Splenectomy for Essential Thrombocytopenia.

Having established methods for the diagnosis of purpura hemorrhagica, the next step was to elucidate the etiology. In this field the names of Frank, Kaznelson, Eppinger and Glanzman are prominent for their contributions. Each of these workers presented different views as to the pathogenesis of this condition. We are indebted to E. Frank for his extensive researches on this subject, for they culminated in the presentation of a well-defined clinical entity. He was the first to show the constant association of a thrombocytopenia in these cases, and he, therefore, designated the disease as "essential thrombopenia." Eppinger suggested the term "thrombocytopenia" because the word represented the true state of affairs—a diminution in the number of thrombocytes. We are equally indebted to Kaznelson for performing the first splenectomy in 1916 for this condition.

A brief summary of the prevailing theories regarding the pathogenesis of this condition may not be amiss. Kaznelson regarded this condition as a thrombocytic purpura due to primary hyperfunction of the spleen. The latter may occur in association with an intact bone marrow. Frank believed that a defect in the production of platelets due to the action of some noxa on the megakaryocytes alone caused this condition. Seeliger (quoted by Piney) has described pathologic changes in the protoplasm of the megakaryocytes in a case of Werlhof's disease. There were many of these cells (about 90 per cent) in the marrow, in which no granules could be found, showing a degradation of thrombocytopoiesis; Glanzman regarded this disease as due to an hereditary weakness or deficiency of the platelets themselves.

Piney has stated that "The acceptance of the view that the megakaryocyte is the site of injury in Werlhof's disease does not involve a denial of the importance of excessive splenic function; it only involves a repudiation of the conception that such an alteration is the primary fact." Piney continues: "The therapeutic measures available in this disease are comparatively successful, but cannot be regarded as being really satisfactory in the absence of a knowledge of the etiologic factors."

A survey of the literature fails to reveal a consistency of cure in all cases following splenectomy. An analysis of a review by Giffin and Holloway of 28 cases of purpura hemorrhagica which were splenectomized, reveals interesting facts. Four cases, or 14 per cent of the patients (excluding two deaths), showed no marked improvement following splenectomy, either from the clinical or hematologic angles. In most of these the platelets were low, and the bleeding time was still prolonged two months after operation. Piney classifies these cases into three groups:

1. Those in which operation is followed by a rapid and persistent rise of the thrombocytes to normal or even to a higher figure; a cure cannot be claimed in any case.

2. Cases in which the number of platelets rise to a figure above normal within a few days of the operation, but in which they fall below the critical value in a very short time.

3. Cases in which splenectomy causes no, or practically no, change in the number of platelets—pointing against spleen as primary site of pathogenic process.

A. W. Spence has recently abstracted 101 cases of purpura hemorrhagica treated by splenectomy. An analysis of the abstract revealed a mortality of 17 per cent, and poor results, that is, a return to the presplenectomy states in 15 per cent of the cases.

The occurrence of the 2 cases herein described has led us to the consideration of a factor not hitherto mentioned in the literature. We refer to the accessory splenic tissue. It is apparent that this feature has been entirely overlooked, and it seems to us that the situation may be somewhat clarified when cases of purpura hemorrhagica are regarded from the standpoint of the presence or absence of accessory splenic tissue.

The object of this paper is to report 2 cases of purpura hemorrhagica, one of which was followed by apparent cure almost three years after splenectomy, and the other still showing symptoms and signs of the disease almost two years after operation.

Case Reports. CASE I.—M. T., female, aged twenty-one years, entered the hospital August 1, 1925, on the service of Dr. Simon R. Blatteis. Her chief complaint was persistent nosebleed for nine hours before admission. Her past history revealed frequent occurrences of purpuric spots appearing after the slightest trauma. For the past few months she has had severe bleeding from the gums. Since February, 1924, attacks of epistaxis were very frequent. Her last attack of epistaxis was so severe that hospitalization was advised.

Examination showed blood extravasations, varying in size, over the upper and lower extremities, right frontal and left anterior triangles of the neck, and petechial spots over both buccal surfaces. The oral and pharyngeal mucous membranes were congested. The gums bled easily under the slightest pressure. The heart and lungs were negative. Abdominal palpation revealed no enlargement of the spleen or liver. Her blood pressure was 128 systolic and 86 diastolic. Eyeground examination was negative.

Laboratory Findings. The patient's hematologic studies since her admission are reproduced on Chart I. In addition, the following examinations were done: Clot retraction, absent; coagulation time, five minutes; differential count: polymorphonuclears, 70 per cent; small lymphocytes, 28 per cent; eosinophils, 2 per cent. The blood Wassermann test was negative; urinalysis, negative; test of stool for occult blood, negative; van den Bergh test for bilirubin (direct), negative; bilirubin (indirect), 2 units. Blood chemical tests (including chlorids, cholesterol and calcium) were normal.

Her condition continued to get worse up to September 5, 1925, when the bleeding time was over one hour, and the platelet count 110,000. Splenectomy was performed by Dr. John Linder on September 5, 1925 and this was followed by a transfusion. A rapid improvement was noted. Her bleeding time fell to normal and the platelet count rose to 940,000 within a period of two weeks. Chart I shows in detail the gradual approach to nor-

mal of the patient's blood picture. Since the splenectomy she has had no nosebleeds, no petechial eruptions, and her general condition at present is excellent.

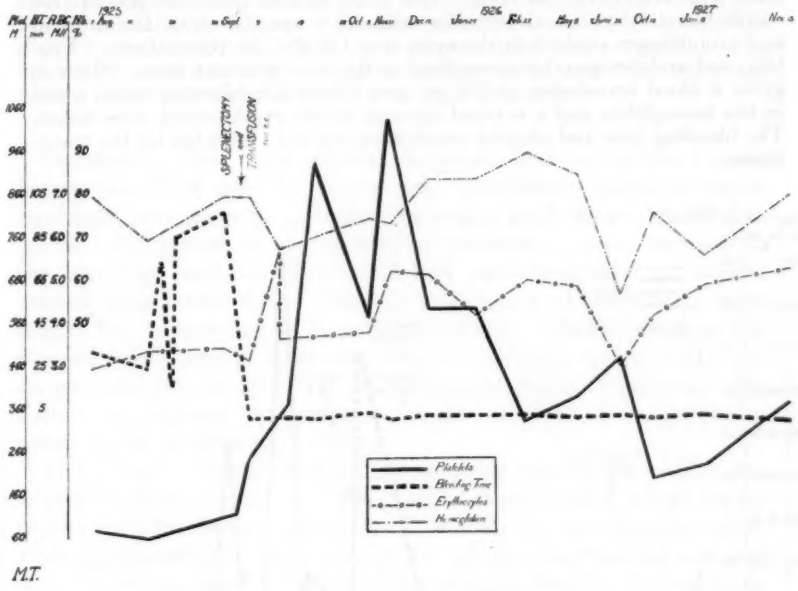

CHART I.

CASE II.—J. B., female, aged seventeen years, was admitted to the hospital April 29, 1926. Her chief complaint was nosebleed for the past four years. Her menstrual periods started when she was sixteen years. The last period lasted ten days and was very profuse. She also complained of headaches, weakness, dizziness, and transient black and blue spots.

Physical examination showed a well-developed, well-nourished young girl, very pale and apparently quite anemic. There were many petechiæ on the buccal mucous membrane and fading purpuric spots on the skin over the abdomen and legs. The right axillary and both inguinal lymph nodes were palpable. The lungs showed nothing abnormal. The heart was negative except for a functional apical systolic murmur. Her blood pressure was 105 systolic and 50 diastolic.

Laboratory Findings. In addition to the hematologic studies on Chart II, the following investigations were made: Clot retraction, absent; coagulation time, six minutes; differential count: polymorphonuclears, 59 per cent; small lymphocytes, 33 per cent; large mononuclears, 3 per cent; transitionals, 4 per cent; eosinophils, 1 per cent. The blood Wassermann test was negative; urinalysis, negative; icterus index, 5; van den Bergh test for bilirubin (direct), negative; bilirubin (indirect), negative; blood, culture, sterile.

This patient was first admitted to the hospital in 1913 at the age of four years. She was suffering from nosebleeds following pertussis. After a short stay in the hospital she was discharged improved, notwithstanding her anemic condition. (See Chart II.)

Her second admission to the hospital was on December 5, 1922, when she was thirteen years of age. At that time she again complained of frequent nosebleeds, some lasting continuously for a whole week. These attacks were followed by headaches, weakness and dizziness. Many purpuric spots were noted over her body. Her stools at that time were positive for occult blood. Her blood bilirubin estimation was 3.3 units, the urobilin and urobilinogen content in the urine was 126 and 54, respectively. Urobilin and urobilinogen determinations on the feces were not done. She was given a blood transfusion of 250 cc. (see Chart II), following which a rise in the hemoglobin and a marked increase in the erythrocytes were noted. The bleeding time and platelet count were not much affected by the transfusion.

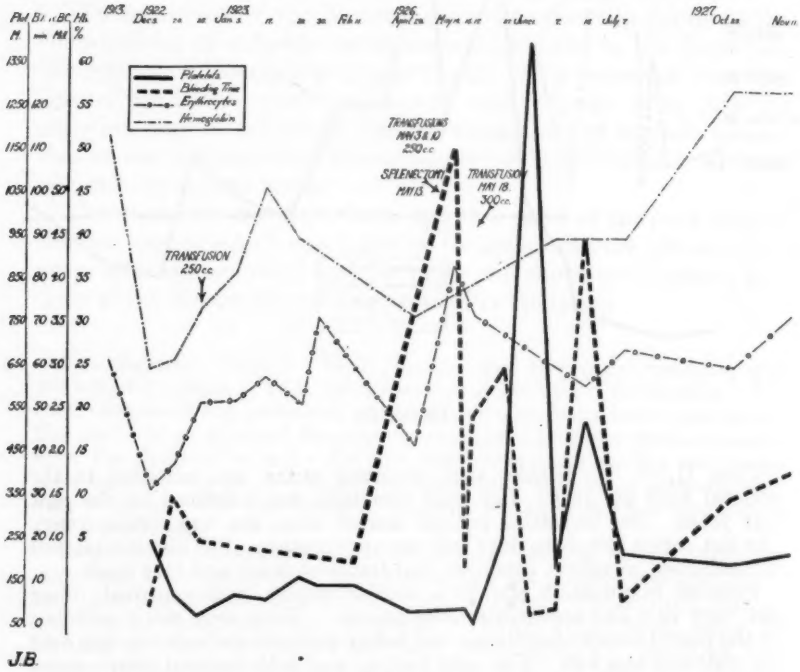

CHART II.

Four years later she was readmitted with the complaints described above. On May 3 and May 10 two transfusions of unmodified blood (250 cc. each) were given. This was followed by a splenectomy on May 13, 1926, by Dr. John Linder. The surgeon recorded the following note on the operative sheet: "There was an accessory spleen about the size of a small walnut anteriorly—not removed." Within four days the bleeding time dropped from one hundred minutes to thirteen minutes, while very little change occurred in the platelet count. On May 18 the patient was again transfused, this time receiving 300 cc. of blood. The number of platelets rose to a normal level, but the bleeding time increased to an hour. On June 1, however, the number of platelets rose to the high level of 1,410,000 with the establishment, for the first time, of a normal bleeding time of three minutes. A week later the platelets dropped to 190,000, while the bleeding time increased

to five minutes. Gradually the bleeding time increased to over thirty-five minutes, while the platelets remained at about the normal level. Clinically, she showed little improvement. At present, twenty-one months after the operation, the patient still has nosebleeds and petechial spots. Her menstrual periods last from six to ten days, although the bleeding is not as profuse. Her bleeding time has again increased to over an hour, while the platelet count is 320,000. The blood shows normal clot retraction. The red cell count is 4,640,000, hemoglobin, 85 per cent, and white cell count 13,600. The blood coagulation time is eight minutes.

Comment. The salient clinical diagnostic features of the 2 cases herein described are the young age, nosebleeds, purpuric spots, weakness and anemia. Hematologically, both cases revealed a marked diminution in the number of platelets, a great increase in the bleeding time, an absence of clot retraction, and an almost normal coagulation time. The first case had a comparatively large spleen, but no demonstrable accessory spleen. The second case had a small spleen and at least one notable accessory spleen which the surgeon did not remove. It is our present effort to influence this patient to undergo an operation for the removal of the accessory spleen noted at time of operation.

The question now arises why the apparent cure in Case I and the relative failure in Case II. Brill and Rosenthal have noted better results with the large spleen cases than with the small spleen cases. They attributed this observation on the supposition that the removal of more reticuloendothelial tissue was responsible for the results in the former. Krumbhaar seems to share the same view. We contend, in view of the researches of Warthin, Binet and others, that in all likelihood small spleens are apt to be accompanied by additional splenic bodies, that is, more reticuloendothelial system—a compensatory phenomenon—whereas large spleens are less apt to have companions.

For this reason it seems to us cure is more apt to follow splenectomy in large spleen cases. The presence of accessory splenic bodies will also explain the persistence of the presplenectomy pictures, even in the apparently cured cases. We were tempted to relegate our Case II in the category of Group III of Piney's classification. The surgeon's operative note having revealed to us "an accessory spleen the size of a walnut" first directed us to its possible causal relationship in the failure to produce a cure in this instance.

One cannot but be impressed with the relative frequency with which accessory spleens are found by the surgeon during operation and by the pathologist on autopsy. Alexander and Romanes state that "the frequency with which the pathologist meets with accessory spleens at necropsies makes it rather remarkable that their presence is rarely noted by the operating surgeon." They quote such authorities as Adami and Nicholls and Shennan as to the frequency

of supernumerary spleens postmortem. The former authorities reported an incidence of 11 per cent. Indeed, Lubarsch states that because of their frequent occurrence they must be included in the normal anatomy of the adult. Accessory spleens may reach the size of a walnut, as described by Shennan, or the size of a tangerine, as described by Temoin. Eccles and Freer report a case of splenectomy where a reoperation after an eight-year interval demonstrated an enlarged spleneculus, whose size, shape, color and consistency were that of the normal spleen.

The location of accessory spleens varies. According to Schilling, the most frequent sites are: (1) Hilum of the spleen; (2) gastrosplenic omentum; (3) great omentum; (4) edge of omentum; (5) splenocolic ligament; (6) pleurocolic ligament; (7) peritoneal tissue along bloodvessels of spleen; (8) pancreas.

Describing them, Alexander and Romanes state: "They may be sessile or pedunculated, and in the latter case several were often found in the pedicle of a larger one"—"disposition en chapelet." Rocher ascribes their distribution to their development in the dorsal mesentery and especially in that segment from which the stomach and pancreas are formed. He appears to regard them as portions of the normal organ which have separated during development. Albrecht, quoted by Osler and McCrae, reports a case in which "an enormous number of supernumerary spleens was found. The normal spleen was in the usual situation, the size of a walnut, with the splenic artery and vein in their normal position." The other spleens were scattered not only in the mesogastrium, but also on the peritoneum; the largest number was found on the mesentery, and transverse mesocolon; there were more than 30 in Douglas' pouch; each of these spleens was enclosed in a separate capsule covered by peritoneum, and exhibited the gross and microscopic structure of splenic tissue. Warthin suggests that this is not simply a congenital condition, but rather a compensatory process of accessory spleen development secondary to a congenitally-deficient primary spleen, or to acquired disease of the spleen.

Supernumerary spleens have been noted by a number of observers. Hance reports a case in which an accessory spleen was found in a hernial sac during the course of an operation. De Teyssieu records a case in which an accessory spleen was discovered on postmortem embedded in the liver of an elderly female lunatic. William Linder records a case in which a splenoma of a supernumerary spleen was found between the layers of the gastrocolic omentum. Observation of similar cases has been reported by Jolly, Lanphear, Temoin and Younge. The patient reported by Alexander and Romanes complained of acute attacks of abdominal pain. These were caused by an accessory spleen situated in the great omentum. W. A. Sneath reported a case of a scrotal spleen which was mistaken for a third testicle. This, of course, could be accounted for embryologically.

Winteler reports an autopsy in which, incidentally, there were found several hundred splenic bodies scattered in the abdomen. The largest measured 2 cm. in diameter. Rocher states that he has frequently, at operations, observed the occurrence of accessory spleens, especially in young subjects. On examination of the bodies in the postmortem room he found that those seen in the infant were in many cases undergoing atrophy and that the splenic tissue was difficult to recognize. These were less red than the others, almost yellow, and of a faded appearance. On the contrary, those of a red color showed the normal structure of the spleen. From the diminished frequency of their occurrence in the adult, he thinks these accessory organs show a tendency to disappear with age. Two, four, or seven of these organs were most commonly met with in each case, but Orth records 400 in one instance.

Accessory spleens are very common in young children. Jolly found them in 25 per cent of a series of 80 children less than seven years old, and Sassuchin (quoted by Gundobin) observed them in 23 cases in a series of 153 autopsies of children under ten years. He found them much more common in newborn infants and sucklings than in older children.

Hempelmann states, in *Abt's Pediatrics:* "Accessory spleens are not infrequently met with in man, usually a small bud of splenic tissue situated between the peritoneal folds near the hilum, but they may appear in any part of the abdominal cavity. In size they usually range from that of a pea to that of a walnut, and their number may vary from one or two to several hundred."

Lederer in his studies on hemal nodes refers to the close resemblance of these structures to accessory splenic bodies. He states: "They look like congested lymph nodes or accessory splenic bodies. Their shape may be that of the spleen. They are bluish-gray in color. On section the resemblance to splenic tissue is quite marked. The pulp is homogeneous, streaked here and there with trabeculæ and spotted with dewdrop-like Malpighian bodies. The parenchyma is surrounded by a well-defined capsule." The terms hemolymph gland and supplementary splenic bodies are used synonymously by Binet in reporting his studies on dogs.

The general incidence of accessory spleens seems to increase in direct proportion to the zeal of the searcher. We have noted accessory spleens in 35 per cent of the cases that came to necropsy, since we began a systematic search for them. In all probability, the figures reported previously have been too low.

The previous contention that the spleen was not solely responsible for the disease because of its recurrence after splenectomy, loses much of its force when one considers the biologic possibility of accessory spleens and hemal nodes, their ability to take over the work and with it the pathic influence of the primary spleen. Alrutz, Nortell, and Piette are of the opinion that the involvement of the

reticulo-endothelial system in thrombopenic purpura is limited to the spleen only. They, however, fail to mention specificially accessory spleens.

The mode of procedure for a splenectomy will have to be modified. It seems plausible that the operation must consist of two phases: (1) The search for and removal of supernumerary spleens; (2) the splenectomy itself. It is, of course, readily seen that many cases will be inaccessible to the surgeon. But as time goes on newer technique may be evolved which will circumvent present difficulties. Having a knowledge of the usual anatomic locations of these bodies, he may readily adopt a specific procedure to fit the individual case.

Conclusions. 1. A brief outline of the historic background of this disease is presented.

2. A review of the available literature of cases treated by splenectomy shows in most instances temporary relief or cure of the purpura. Sooner or later they relapse into the presplenectomized states, which may or may not be modified.

3. An hitherto unstressed feature is presented which may be the reason for the general failure of splenectomy in the presence of unnoticed, or if noted, unmolested accessory splenic bodies. Such accessory splenic structures may undergo compensatory hypertrophy and gradually assume the pathic functions of the primary spleen.

4. The prevalence of the incidence of accessory spleens is brought out by not a few observers—pathologists and surgeons.

5. Two cases are presented which exemplify thrombocytopenia without accessory spleens and thrombocytopenia with accessory spleens.

It is hoped that this communication will serve as a forerunner of further investigation along these lines.

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GASTRIC POLYPOSIS.

A Report of Two Cases with a Review of the Literature.

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and

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Chicago.

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Gastric polyposis is known to occur rather infrequently, but in recent years the attention of the clinician has been directed to this condition by the routine roentgenologic examinations of the stomach. It is of interest to record that although Cruveilhier first reported a case in 1833, it was only as recent as 1909 that Wegele made an antemortem diagnosis, and in 1919 Balfour recognized and described the condition by Roentgen ray.

We wish to report 2 cases which have come under our observation.

Case Reports. Case I.—E. L., aged thirty-three years, female, married, was admitted March 25, 1927, to the Michael Reese Hospital (service of Dr. Solomon Strouse), complaining of burning pain in the epigastrium,

nausea, belching, loss of weight, pallor. For the past nine years the patient had "stomach trouble." Her chief complaint is pain in the epigastrium, at present independent of food intake, but made worse by the same. In addition, she spoke of a pressure in the epigastrium which came and went and was independent of food and bowel movements. She stated that she had attacks of stomach trouble every two years (in the past nine) and had been on a diet of milk and crackers and a "Sippy cure." At times this gave her some relief, but pain was constantly present. When her trouble first started, it began suddenly with pain in the abdomen and vomiting of blood. Since then she has not vomited blood and her symptoms were as above.

The present attack began three weeks before admission. The pain in the epigastrium was more severe than formerly. Nausea was also present, especially on riding up elevators. She has not had diarrhea at any time, but has noticed that the stools were black, and has also seen undigested food in the stools. The pallor, which is striking, has been present for years. The previous history is negative.

Physical examination revealed a malnourished woman, slightly wasted, with pallid face and lips. There was no jaundice. The heart and lungs were normal. The abdomen was soft; no masses were palpable but there was definite tenderness 2½ inches above the umbilicus in the midline. Liver and spleen were negative. Gastric analysis (Ewald meal): At the end of forty-five minutes showed no free acid; total acid, 22. When repeated there was no free acid; total acid, 17; no Boas-Oppler bacilli, no lactic acid; Blood present. Motor meal showed no retention at the end of six hours. Stools were dark brown in color, no blood present. Blood examination showed hemoglobin 80 per cent, red cells 4,300,000, white cells 8000. The blood Wassermann was negative.

Roentgenologic Report. The roentgenogram confirmed fluoroscopic findings of heavy thickened rugæ in the cardia of the stomach characteristic of polyposis.

The clinical impression was that of an intrinsic gastric lesion, probably malignant in character, and this was based on the persistent absence of free hydrochloric acid in the stomach contents and the presence of blood, the general picture of anemia, and loss of weight. Operation was advised.

On opening the abdomen, the stomach presented and had the appearance of a placenta, being large, cyanotic and boggy. The lower pyloric end was perfectly normal, but starting at the pyloric antrum, there was a thickening of all the walls, a marked hypertrophy of the glands in the stomach extending up to the cardia. A subtotal gastrectomy was performed. The patient made an uneventful recovery and at present is at work.

Pathologic Report (Dr. O. Schultz). Gross appearance: The stomach, when opened along the lesser curvature, measures 25 cm. in length, 14 cm. across at the fundus and 8 cm. across at the pyloric end. Beginning about 2 cm. from the upper edge, there is an extreme hypertrophy of the rugæ which are arranged in large irregularly longitudinal rows. In some places the rugæ measure 3 cm. in depth. The area of hypertrophied mucosa is mostly in the greater curvature and there still remains a thin strip of flat mucosa on the lesser curvature. This forms a path about 2 cm. across and extends down to the pyloric end where it becomes continuous with the antrum. The antrum measures 3 cm. in length. Even in this relatively flat portion of the stomach there are several prominent rugæ. In the flattened portion as well as over the rugæ, there are numerous closely packed, slightly nodular elevations, about 3 cm. across. On one of the rugæ in the midportion there is a small hemorrhagic zone, and a number of other smaller erosions are present. The mucosa toward the upper portion contains a number of punctate hemorrhagic areas. The entire mucosa is

FIG. 1.—Roentgenogram of Case I.

FIG. 2.—Roentgenogram of Case II

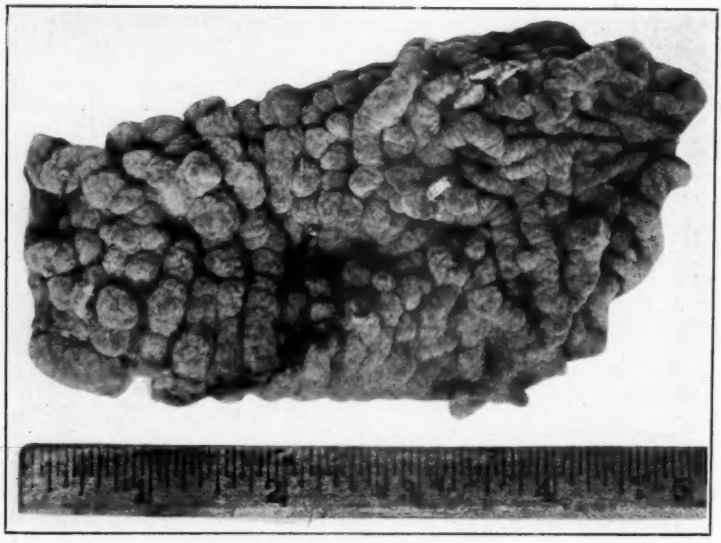

FIG. 3.—Gross specimen showing polyadenoma en nappe. Case II.

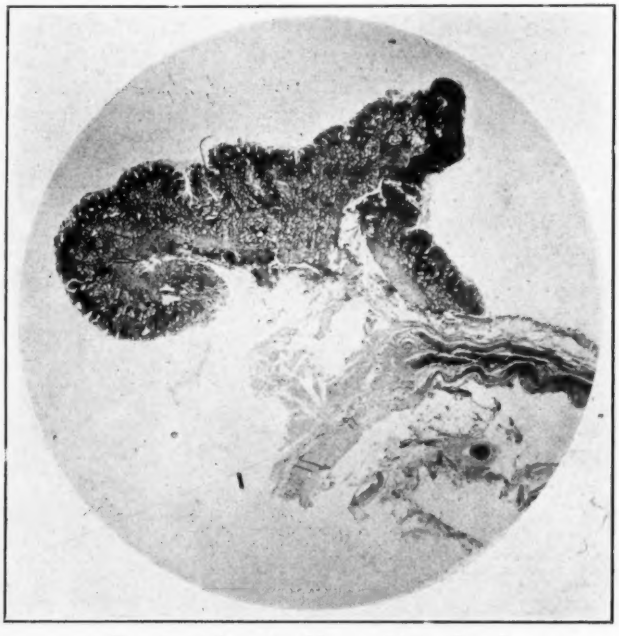

FIG. 4.—A hypertrophic ruga × 9. Case I.

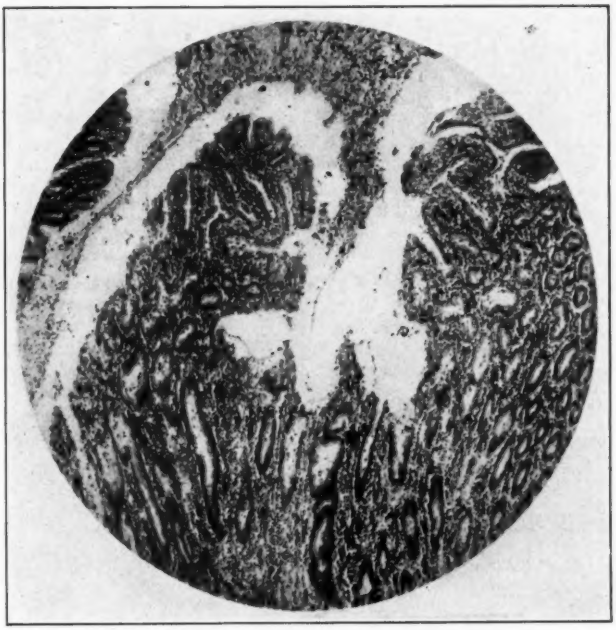

FIG. 5.—Cellular infiltration and fibrous-tissue changes × 60. Case I.

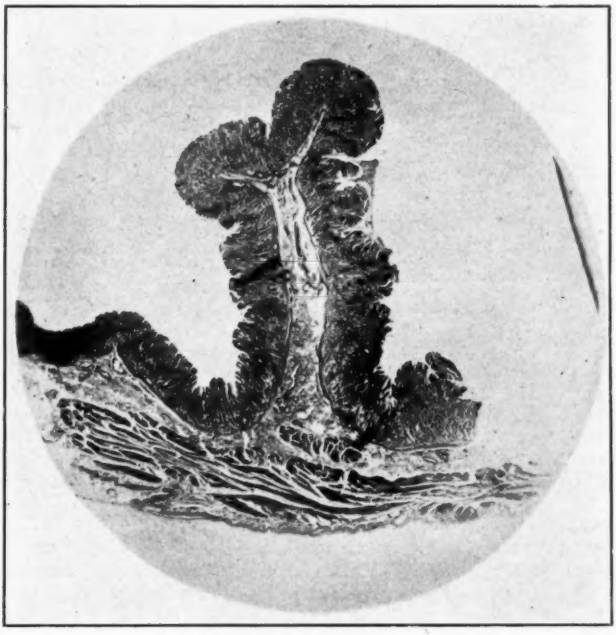

FIG. 6.—A hypertrophic ruga × 6. Case II.

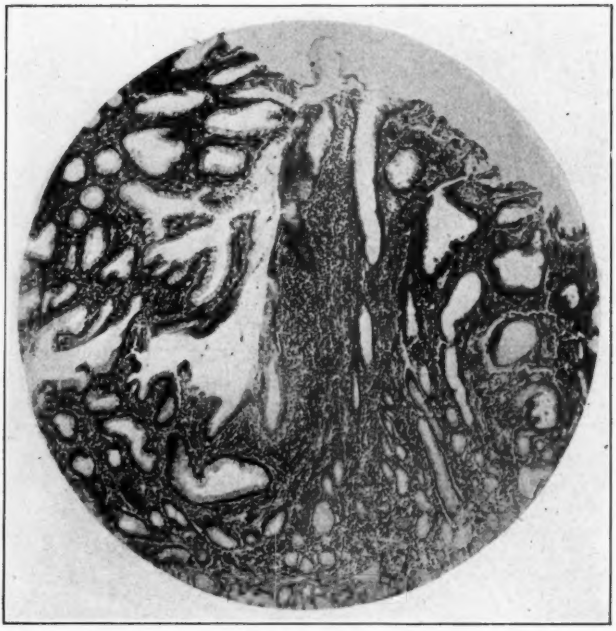

FIG. 7.—Showing dilatation of glands and cellular infiltration × 60. Case II.

covered with a thin layer of mucus. The serosal surface is everywhere smooth. In the fixed preparation the thickened portion of the stomach wall is slightly over 2 cm.

Microscopic Findings. In a section from one of the smaller hypertrophied rugæ, the mucosa is seen to be very regularly disposed and of a practically equal thickness throughout. The glands are straight and thin and are not dilated. The interstitial tissues are rather markedly infiltrated by large numbers of plasma cells, a few lymphocytes and a scattering of leukocytes. Here and there leukocytes are collected in small groups. There is a slight diffuse increase of interstitial connective tissue. The small vessels of the stroma are in places dilated. The lymphoid follicles of the mucosa are rather numerous and large, but contain only poorly outlined germinal centers. The rest of the structure of the stomach wall is without evident change. The muscularis mucosæ is distinct. Some of the bundles of the muscle layer are separated by a small bit of fibrous tissue. There is no reaction in the serosa. In some places the gastric glands are closely packed, particularly where the section curves. The other sections taken from the tip of one of the longest rugæ shows essentially the same picture. In the outer surface there is a good deal of mucoid material containing some broken down cells. Several other sections taken through the stomach—one of them through the portion of stomach which is free of hypertrophied rugæ, show a similar picture.

CASE II.—E. L., aged thirty-eight years, male, was admitted March 12, 1926, complaining of pain in the epigastrium. This pain was first noticed by the patient two years ago. It had been present constantly since that time but became worse in the past weeks. It had no relation to meals, sometimes coming before or after, and was not relieved by food, alkalies, milk or cream. No jaundice was present. The previous history is not of interest.

Physical examination showed a well-nourished man, of good color. The heart, lungs and abdomen were negative; liver and spleen were not palpable.

An Ewald test meal showed no free acid, no blood. Stools were negative for blood. Blood examination showed hemoglobin 65 per cent; red blood cells, 3,200,000; white blood cells 5600.

Roentgenologic examination showed the following: STOMACH: The stomach is orthotonic in type, the greater curvature extending two fingers below the crest line. There is a moderate amount of fluid present. It is freely mobile and there is good persistalsis. The pylorus is serrated. Motility, four and a half hours. DUODENUM: The bulbus duodeni at no time fills out well. At two hours it appears definitely defective. After the administration of atropin the cap fills out fairly well but the pylorus maintains the same serrated appearance. ROENTGENOGRAPHIC: The films confirm the fluoroscopic findings presenting a defective pylorus and bulbus duodeni. The gall-bladder films do not reveal a shadow.

Operation was advised.

On opening the abdomen the lower half of the stomach contained many soft nodules which could be felt through the stomach wall. There was a definite multiple polyposis of the lower half of the stomach.

The patient made an uneventful recovery and was discharged from the hospital.

He returned to the hospital December 28, 1926, for removal of a foreign body of the hand and for transfusion. He presented a picture simulating pernicious anemia: hemoglobin 65 per cent (Dare), red cells 2,400,00, with marked anisocytosis, a few poikilocytes and a few macrocytes. He was discharged on March 25, 1927, improving.

Pathologic Report. Gross: Section of stomach unopened measures 12 by 6 by 2 cm. When inverted the mucosa exposed is seen to have markedly polypoid arrangement, especially at the pyloric end. The rugæ are hypertrophic and enlarged, the surface irregular, rugated on themselves. Numerous small polyps are present on them. Polypoid effect is much diminished near the cardiac end. The serosa is smooth; no areas of ulceration are seen. Also present is a strip of stomach measuring 5 by 3 cm., probably a trimming of the wound. In this portion polypoid arrangement of the mucosa is not apparent.

Microscopic. The mucosa of the stomach is infiltrated by a large number of round cells and there is an increase of fibrous tissue around the glands. Many of these glands are dilated and almost cystic. The mucosa is slightly undulating. No ulcers are noted. In other sections the dilatation of the glands is more marked and where these are present the cellular infiltration and fibrous change in the mucosa are most marked beneath the surface epithelium. In one section is quite a large amount of hemorrhage beneath the surface epithelium and into the underlying submucous glands. In this section the polypoid arrangement of the mucosa is more manifest, the polyps being large and round with very narrow crevices between them.

Incidence. Though this condition is considered rare, Brunn and Pearl, in a very exhaustive study, have found 84 cases. Eusterman and Senty believe that this is the rarest form of benign tumor of the stomach. Eliason and Wright, in 8000 autopsies at the Philadelphia General and University of Pennsylvania Hospitals, state that they found "polyps" (a term indicative of the gross physical character rather than microscopic picture) in 32 per cent of the gastric tumors, while only 1 case of true polyposis. Versi collected reports of 55 cases of polyps of the digestive tract, 4 of which were in the stomach. Tilger, as Jesse Myer pointed out, could find only 14 cases in a series of 3500 cases that came to autopsy. In the Obuchon Krankenhaus there were 4 cases in 7500 autopsies. Balfour described his case as the first in 8000 gastric operations. Carman encountered 2 in 50,000 gastrointestinal radiologic examinations. On the other hand, Sielman and Schindler state that in 300 gastroscopic examinations they found 20 malignant and 4 benign tumors. The discrepancy of incidence in the literature appears to be one largely due to the criterion or definition of "polyps." Jesse Myer quotes Elistein who in 1864 found 14 cases of stomach polyps in 600 autopsies and was able to collect reports of 8 others from the literature. Of these 22 cases the author felt justified in speaking of polyposis in only 3; these presented as many as 200 polyps which varied in size from a pea to a bean. Ruggle stated that in 1917 only 4 cases of polyadenoma *en nappe* had been reported in the literature. In 1926 Brunn and Pearl raised this figure to 5. Both of our cases fall in this group.

Etiology. Very little is known as to the causative factors in this condition. It is found in individuals past middle age although Petrow reported 1 case at twenty years. Both of our cases were in their thirties. Struthers gives the following ages for 20 cases: 4

between seventeen and thirty years, 8 between forty-one and fifty years, 2 between fifty-one and sixty years, 3 between sixty-one and sixty-eight years, 2 between sixty-nine and seventy-five years.

As to sex, they are about equally divided. In Brunn and Pearl's figures there are 29 males and 30 females. Struthers gives 10 males and 10 females. Even in our small series of 2 cases, they were equally divided. None of the authors state whether or not this condition is confined to any one race. Practically all the early writing was done by the French and Germans. Where the nativity or extraction is mentioned it usually is of Nordic origin. Both our cases occurred in Scandinavians. Eliason and Wright state that 80 to 90 per cent are found in the laboring class.

There are several theories as to the direct cause of gastric polyposis. Wechselmann believed it to be of congenital origin, stating that the polyps emanate from epithelial fetal anlagen separated during development. He found a familial tendency in 50 to 60 per cent of cases. Myer also believed it to be due to congenital malformations and that the epithelial reaction is secondary. He noted family relationship in his cases. Hertz, Mueller and Roth (quoted by Rosenberger) all consider polyposis a hereditary disease. Brunn and Pearl and Struthers could find no such relationship. In one of our cases the patient stated that several members of her family had "cancer" of the stomach.

The greater number of authors point to chronic gastritis as an underlying factor in the production of gastric adenopapillomata. Among some of these were Menetrier who stated that each case presented chronic inflammatory changes. Hauser, Cornil, and Versi also demonstrated these findings. Eliason and Wright state that gastritis was a concomitant feature in their cases and that the hypertrophic form predominated. Basch noted this in all his cases. Konjetzny had noted the gradual transition from chronic gastritis through adenoma to carcinoma. Zoble quoted by Bryan found a large number of megastoma intestinales in gastric polyps. Otto reported an adenoma caused by a splinter of wood. Ishibashi and Ohtani experimentally produced papillary adenoma in the stomach of rabbits by feeding them coal tar. Fibiger and Wassink have done this by feeding a certain nematode to animals. Gastritis was noted in both our cases.

On the other hand, there are a number of men who do not believe that gastritis is a necessary part of polyposis. Pearl and Brunn found chronic inflammation in only 32 per cent. Hauser claims that it is due to primary degeneration of epithelium and that chronic infection is secondary. Huber attempted to show that they were the result of a general systemic lymphatic hypertrophy.

P. W. Brown (quoted by Struthers) believes this condition to be due to the result of metabolic changes which so lower the resistance that the mucosa is an easy prey to bacterial invasion. Other pos-

sible causes put forth are alcoholism, atheroma of the gastric vessels, arteriosclerosis, and syphilis. None of these conditions are constant, nor are they found even in a majority of cases.

Other conditions found in association with polyposis are chronic pleurisy, pulmonary tuberculosis, cerebral hemorrhage, atheroma of the vessels, and syphilis.

Pathology. Of the benign tumors of the stomach, polyposis form the most important group. Menetrier's classification which is still accepted is as follows: 1. Polyadenoma *polypeux*. 2. Polyadenoma *en nappe*.

In the first group, the ducts are principally involved. The tumor is distinctively lobulated and cysts are more common owing to the obstruction of the excretory ducts. The second class is usually located in the fundus. There is little lobulation and the cysts are few in number or absent. The hypertrophy forms a raised, well-demarcated plaque. This type is rare and only 5 cases are reported in the literature. We believe that both of our cases fall in this group.

Hayem described a third type as Brunnerian adenoma. These glands are of the duodenal type and are supposed to be the result of misplaced duodenal cells during embryonic life.

On opening the abdomen, one feels a doughy mass which give the sensations of a bag of worms. A number of soft lymph glands somewhat enlarged are found near the attachment of the greater curvature. When the stomach is opened, the tumor is soft in consistency and varies in size from a few centimeters in some cases to extensive involvement in others. The color depends upon the vascularity and may be grayish or deep red. The folds are deep and the general appearance resembles that of brain cortex. On the surface there are, as a rule, hemorrhagic areas of ulceration or a thick mucus of egg-white consistency or both. In the polyadenoma *polypeux* great numbers of polyps may be seen. They may be pedunculated or attached to a broad base.

On serial section, the stomach mucosa shows gradual increase from normal thickness to tremendous hypertrophy. The general picture is that of hypertrophied gastric glands and congestion of the bloodvessels. Otherwise there is no departure from the normal. The connective tissue and musculature take no part in the growth.

Symptoms. Gastric polyposis may go along for a number of years without causing the patient any discomfort. Wegele's case complained for twenty-nine years, Menetrier's twenty-five, and one of Brunn and Pearl's for twenty years. On the other hand, the symptoms may be very severe depending on the size, location and nature of the growth. About the first sensation the patient experiences is a sense of pressure or weight in the region of the stomach. This usually progresses to marked discomfort and abdominal distress. Pain is the most constant finding. It is practically always

located in the epigastric region. Its character is cramplike and burning. In some cases it is relieved by food while in a number it is in no way influenced. The other symptoms are anorexia, loss of weight, vertigo, anemia and nausea. Headaches after eating are often encountered. Vomiting does not often occur although nausea is a constant complaint. The vomitus may contain the characteristic egg-white mucus, blood, or rarely pieces of tumor tissue. Higgin's case was diagnosed by this means.

Hemorrhage is practically always encountered. This may be due to the extreme vascularity of the tumor or to erosion of the superficial mucosa. This blood is usually found in the vomitus but is seen in the stools in a fairly large percentage of cases.

Achylia is a constant finding. Diarrhea may develop and may be so severe as to mask the nature of the gastric pathology.

When the tumor is situated at the pyloric end and is pedunculated, prolapse may result causing signs and symptoms of obstruction, such as dilatation of the stomach, vomiting, shock, etc.

In 1896, Stevens reported a case of gastric polyposis in an epileptic in whom the aura was referred to the stomach.

Physical Examination. Physical findings are usually absent or at least not characteristic. The patient is as a rule well nourished but anemic. The mucous membrane is pale. In a few cases a palpable mass may be found in the epigastrium and there may be slight tenderness.

Laboratory Findings. The gastric analysis reveals an absence of free hydrochloric acid and a low combined acidity. Lactic acid may or may not be present. As noted above, mucus of an egg-white appearance may be aspirated. Free blood is occasionally seen in the gastric contents. The red count is practically always below normal, although in the majority of cases it is above 4,000,000. At times it may be as low as 2,000,000 or 3,000,000. The hemoglobin is also low and in most cases corresponds to the drop in the red count. The white count and differential are normal.

Roentgen Ray. The most characteristic finding in gastric polyposis is the Roentgen ray picture. This is in sharp contrast to the findings in the other benign gastric lesions. There is a mottled area on the site of the lesion. This mottling is produced by numerous circular areas of lessened density giving the appearance of a bunch of grapes or a sponge. On fluoroscopy, the barium can be seen to trickle through and around the numerous masses. On slight pressure this mottling is increased. The greater curvature border in this area is scalloped. The wall is not infiltrated and although the peristaltic waves do not enter through this area, they approach it very closely. In some cases the greater curvature forms a continuous line through the mass. The rugæ immediately surrounding this are usually more marked than in the normal. There is rarely any retention.

Diagnosis and Differential Diagnosis. The rarity of the lesion makes it one that is frequently overlooked. There is nothing particularly characteristic in the clinical symptomatology which might direct attention to the diagnosis of gastric polyposis. Jesse Myer says that gastric polyposis may be present in a patient with acute gastric hemorrhage, achylia gastrica, increased gastric motility, abnormal mucus production of egg-white consistency. To this may be added the general appearance of well-being which is out of proportion to the findings and the characteristic mottled appearance of the roentgenograms. The problem of diagnosis is one of differentiation from chronic gastric ulcer, carcinoma of the stomach, sarcoma and syphilis of the stomach.

Brams has reported a case in which the picture resembled a colitis with severe diarrhea. In chronic gastric ulcer the presence of hyperacidity, and the relief of pain by food intake are contrasted with the absence of free hydrochloric acid and the failure of relief of pain in gastric polyposis. Carcinoma of the stomach occurs in an individual past middle age. The duration is relatively short. Blood is present in the stools constantly. In polyposis, we have a relatively young individual in a general fair state of nutrition, no free hydrochloric acid in the stomach contents. Blood is found in the stools only occasionally. The gastric defect in carcinoma is more often annular, involving both curvatures, the walls are infiltrated and peristalsis is absent. Sarcoma of the stomach is likewise rare and may offer greatest difficulty. If skin or muscle metastases are present, or tumor tissue from stomach aspiration is obtained, the diagnosis is made clear.

Syphilis of the stomach may simulate gastric polyposis, even as to the roentgenologic findings. In one of our cases we mentioned this as a possibility. Associated findings such as negative Wassermann and negative response to treatment will rule out lues. Other conditions to be excluded are extragastric tumors and foreign bodies such as hair balls in the stomach. The roentgen ray properly interpreted furnishes the best and earliest clinical diagnostic aid in the recognition of gastric polyposis.

Complications. Among the complications which may arise is prolapse of a pedunculated tumor into the pyloric opening. This, of course, only occurs if the tumor is situated near the pylorus. The symptoms are violent paroxysms of pain, nausea, retching and vomiting. The vomitus is usually blood-streaked. There is also distention of the stomach and retention of food. In many cases this is temporary but returns, producing a vicious circle. Gassman reports the possibility of fatal hemorrhage as a complication. Mills states that 4 out of 20 cases of gastric polyposis were associated with carcinoma. In each case the cancer was at or near the pylorus. One's first thought is that these are secondary carcinoma implanted in the polyps. The more probable view is that the cancer is a

malignant transformation. Finney and Friedenwald found carcinomatous degeneration in both their cases.

Treatment. Pearl and Brunn employed Roentgen ray therapy in one of their cases and noted improvement. Struthers noted that one of his cases was relieved for three months but the symptoms returned more severely than ever. Douglas attempted to use radium. Most of the cases were treated by radical operation: resection. When the gastric pathology permits, we are of the opinion that gastric resection is the operation of choice. It is to be remembered that the picture presented by a great many benign tumors is that simulating malignancy; hence these conditions are often considered inoperable because of "the size" and "the degree of involvement." We would direct attention to the necessity of careful clinical and roentgenologic interpretation and, where the anatomic condition permits, advise surgery: preferably gastric resection in the manner of Polyá.

Summary. A report is made of 2 cases of gastric polyposis, polyadenoma, *en nappe*, thus increasing the number reported to 7. The clinical picture of gastric polyposis while not definitely characteristic is suggested by the story of a chronic gastric discomfort, repeated gastric hemorrhages, achylia gastrica, increased or normal gastric motility, abnormal amounts of gastric mucus of egg-white consistency, the general appearance of well-being and a characteristic mottling of the gastric roentgenogram. The problem of clinical diagnosis is one not only of recognition but of differentiation from chronic gastric ulcer, gastric carcinoma, gastric syphilis, achylia gastrica. Where the extent of involvement permits, gastric resection after the manner of the Polyá resection is advised.

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DIFFERENTIAL DIAGNOSIS OF SURGICAL FROM NONSURGICAL JAUNDICE BY LABORATORY METHODS.

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Recent articles by Colp[1] and by McVicar and Fitts[2] indicate an increasing realization of the clinical value of the knowledge that can be derived from the van den Bergh and other biliary tests. For the present, our chief interest lies in the utilization, by the surgeon, of the information that can be supplied by the laboratory. There are few fields of surgery which offer such large returns on coöperation between the laboratory and the surgeon as do the biliary diseases. Proper correlation of the clinical and the laboratory findings will enable us to determine which cases are suitable for surgery at an early stage; to operate early and to decide without delay on the proper operative procedure. Thus there will be, in the surgical cases, a lower death rate and less of the permanent tissue damage which persistent jaundice causes.

Colp states that his cases which had a smooth convalescence were icteric nine days or less prior to operation; those which developed postoperative complications averaged eleven days of jaundice and those which succumbed had been icteric twenty-four days prior to

surgical intervention. McVicar and Fitts give the following essentials to a classification of jaundice as surgical or nonsurgical: (1) The reaction of the jaundiced serum to the van den Bergh reagent, whether direct or indirect; (2) the height and behavior of the serum-pigment curve, as determined by the van den Bergh test or the icterus-index method; (3) the quantity of bile reaching the intestines, as determined by siphonage of the duodenal contents and (4) the presence or absence of pain and its character when present. To these we would like to add a fifth, which we believe is definite in confirming obstruction to the common duct. That is, the presence of bromsulphalein in the duodenal contents thirty minutes after its administration. If it is present, complete obstruction does not exist.

We have followed the line of thought of these writers in studying a group of cases with varied lesions of the biliary tract and, in addition, have employed the bromsulphalein test, in an effort to determine the amount of damage sustained by that organ, or to confirm extrahepatic obstruction.

The laboratory is now able to help overcome many obstacles to the rapid classification of patients with jaundice into surgical and nonsurgical. The pre-operative laboratory study affords an opportunity for measuring the amount of liver damage and this study may justify withholding surgical intervention in certain types of cases. The pre-operative treatment may be begun at the time the laboratory study is undertaken and utilized in counteracting factors peculiar to jaundice which may threaten the safety of operation or success of the surgical procedure. The pre-operative treatment should be directed toward increasing the patient's alkaline reserve, protecting the liver by the judicious use of glucose and supplying the patient's tissue with sufficient fluid. At this time calcium salts may be given to control the tendency to postoperative hemorrhage. The surgeon should keep in mind the danger of acute biliary suppression from a too rapid and continued decompression of the distended duct system as an ever present possibility. The classification of jaundice by McNee is believed to be sufficient to meet the need of the clinician and the surgeon. The types are: (1) Obstructive; (2) toxic and infective and (3) hemolytic. The van den Bergh and bromsulphalein tests will allow the division of all the cases of jaundice into one of these three types.

In obstructive jaundice, the delay in the elimination of bromsulphalein is very definite and of great value in diagnosis when taken in conjunction with the van den Bergh test. Following the introduction of bromsulphalein, it has been our practice to siphon the duodenum in order to obtain samples to test for the presence of the dye. If it is present, the common duct admits leakage. This test is of value following operation for relief of obstruction in estimating the patency of the duct. In malignancy of the liver the test

is of value in determining the amount of liver-tissue damage. Histologically, liver sections show that the immediate direct reaction has occurred only where there was evidence of blocking of the common duct or of the bile capillaries. In those cases where we have considerable impairment of liver function and yet there is sufficient liver tissue present to get rid of the bilirubin without jaundice, the bromsulphalein is of much value in estimating this liver damage.

In malignancy of the liver one may expect to find a low retention of bromsulphalein dye in comparison with the findings in obstructive, toxic or infective jaundice (Dickens). This is consistent with the autopsy findings. This is explained by the fact that malignancy may involve only a portion of the liver tissue and its intrahepatic duct system, leaving the remainder free to secrete the dye, while in toxic and infective jaundice the process is more generalized. We believe that one may, by observing the gradual increase in the retention of the dye and serum bilirubin and careful evaluation of all the symptoms, note with a fair degree of accuracy the progressive involvement of the liver by the malignant growth. The autopsy findings, in the cases now being reported, would seem to support this view. Cole, Copher and Graham[3] state: "We were surprised to find that patients suffering from carcinoma of the liver, whether primary or metastatic, reveal a relatively low retention, the average figure being 28 per cent one-half hour after the injection." Our average figure for retention at the end of a half hour was 27.3 per cent, for the 3 cases of malignancy of the liver reported in this paper.

We have observed that, in jaundiced patients, if the blood sugar and blood chlorids are decreased to approximately 75 and 300 mgm. respectively per 100 cc. of whole blood, symptoms of tetany developed and the patient soon became comatose; and that, if these substances were not raised to their normal, the patients died. This is believed to be an important observation and not an incidental finding, as it occurred in malignancy of the liver, occlusion of the common duct by stone, syphilis of the liver and delayed chloroform poisoning but did not occur in acute cholangitis. With this factor in mind, glucose and sodium chlorid were administered to a postoperative patient who was in coma and had symptoms of tetany with a low chlorid and blood-sugar finding. When the blood sugar and chlorids were raised to their normal, coma and tetany disappeared. We have not yet collected sufficient evidence on clinical cases of jaundice with liver damage to justify a conclusion in regard to this observation. We do, however, consider that a fall in blood sugar with a coincident fall of blood chlorid in jaundiced patients is of grave prognostic import, demanding urgent treatment to restore these substances to normal.

The following cases, which have recently been under our care in the U. S. Naval Hospital, were selected to illustrate the points of our argument.

Case Reports. CASE I (see Fig. 1).—Obstructive type of jaundice, common duct penetrating tumor mass. A man (No. 26740), aged twenty-eight years, with embryoma of the testicle and metastasis to glands at hilum of liver, found at exploratory operation and at autopsy.

April 21, 1927, the van den Bergh reaction was immediate and direct with a quantitative finding 4.33 per 100 cc.

May 1, 1927, van den Bergh had increased to 6.2 per 100 cc.

May 4, 1927, blood chemistry, N.P.N., 41; urea nitrogen, 19; creatinin, 1.3; sugar, 75; and the van den Bergh had increased to 10.1.

May 10, 1927, van den Bergh was direct, immediate with a quantitative reading of 13.8 per 100 cc.

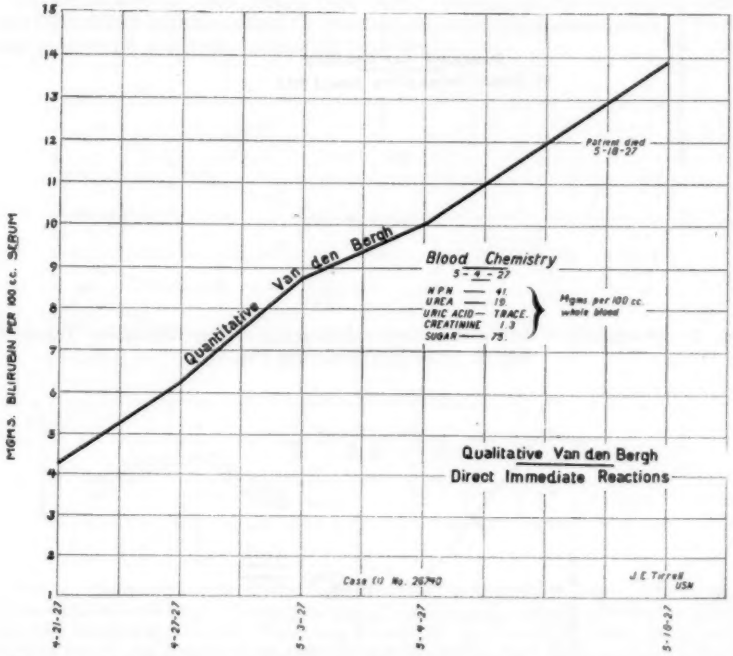

FIG. 1.—Obstruction of the common duct by extrahepatic tumor. Note the steady rise of serum bilirubin when there is complete obstruction of the common duct.

May 18, 1927, death occurred. The autopsy showed the stomach, pancreas and duodenum pushed forward by a large, lobulated, indurated mass which extended from the liver below the umbilicus. The liver was greatly enlarged and extended below the umbilicus. The common duct penetrated the tumor mass. Microscopically, the liver showed areas of extensive infiltration, destruction and compression of liver tissue. Pathologic diagnosis was chorioepithelioma, villous type with parenchymatous degeneration. It was noted that, on section of the duodenum, a probe could be passed through the common duct without meeting obstruction. This case leads us to believe that, with malignancy involving a large part of the ducts within the liver, we may have a direct and immediate van den Bergh reaction, indicating obstruction, even though the extrahepatic ducts are patent. The dye retention in this case was at one time 82 per cent at the end of

thirty minutes. This patient exhibited symptoms of coma and tetany before death.

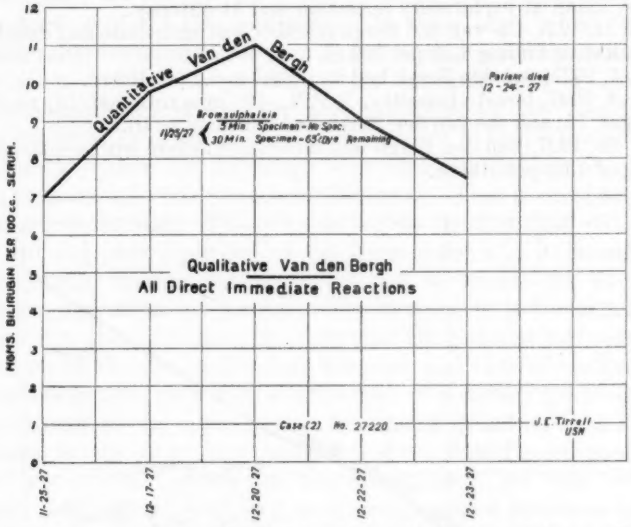

FIG. 2.—Malignancy of liver with extensive destruction of liver substance. Terminal drop in serum bilirubin. See Fig. 3.

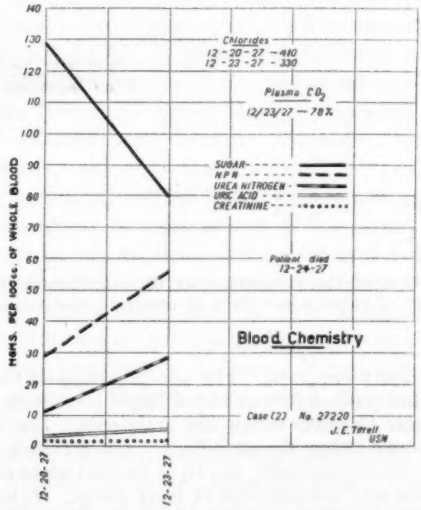

FIG. 3.—Malignancy of liver, showing persistent drop in blood chlorids and blood sugar. Coma has occurred in all our cases when the blood sugar fell to 80 and blood chlorids to 330. This coma was not due to acidosis since the plasma CO_2 was 78 per cent in this patient. The coincident fall of sugar and chlorids is of grave prognostic import. It demands the restoration of these substances to the normal level.

CASE II (see Figs. 2 and 3).—Obstructive type of jaundice, due to pressure on ducts by a tumor outside the liver.

A man (No. 27220), aged forty-five years, with progressive, painless jaundice. On admission, he was deeply jaundiced, with liver considerably enlarged. The van den Bergh test gave the direct immediate reaction with a quantitative finding of 7 mgm. per 100 cc. On November 11, 1927.

December 17, 1927. The van den Bergh was direct and immediate, quantitative findings were 9.7 mgm. per 100 cc. and no bile could be obtained from the duodenum.

December 20, 1927, van den Bergh direct immediate, quantitative 11.5 per 100 cc.

December 23, 1927, after transfusion of 500 cc. of blood by the citrate method and 200 cc. of salt solution administered intravenously, the van den Bergh quantitative was 7.5 per 100 cc.

On December 24, 1927, death occurred. This case shows the usual course and laboratory findings when the extrahepatic ducts are obstructed. There was persistent, painless, increasing jaundice.

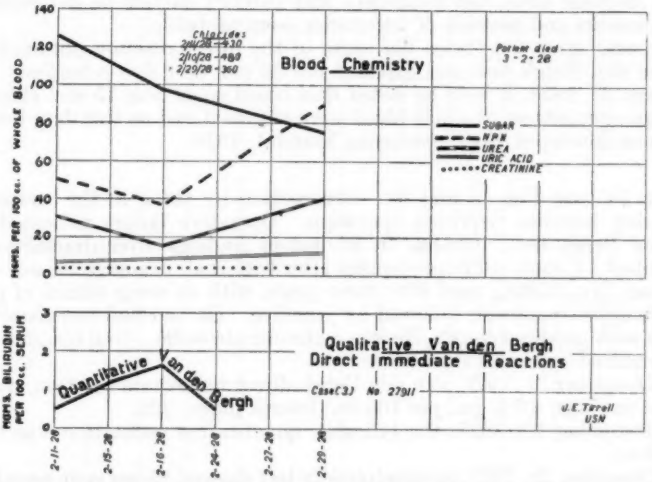

FIG. 4.—Primary cancer of the bronchus with metastasis to liver. Obstruction of the right hepatic duct. Coma and tetany came on when the blood chlorids fell to 360 and blood sugar to 80. This case illustrates the fact that, when malignancy obstructs only one hepatic duct, the van den Bergh reaction increases but does not give a steady rise. Also, the dye retention in such cases may be low, 20 per cent in this patient.

CASE III (see Fig. 4).—Primary cancer of bronchus with metastasis to liver and extensive destruction of liver substance.

A man (No. 27911), aged forty years, with painless enlargement of the liver and beginning jaundice. Liver was nodular on palpation.

On February 11, 1928, van den Bergh direct, immediate, quantitative finding was 4.4 mgm. per 100 cc. Blood chemistry, N.P.N., 50; urea nitrogen, 28; uric acid, 3; creatinin, 1.7; blood sugar, 127; and chlorids, 430.

On February 13, 1928, feces negative for bile.

On February 14, 1928, van den Bergh direct immediate was 10 mgm. per 100 cc. Bromsulphalein showed 50 per cent retention at the end of five minutes and 20 per cent at the end of thirty minutes.

On February 15, 1928, van den Bergh quantitative findings was 10.6 mgm. per 100 cc. Blood chemistry N.P.N., 38; urea nitrogen, 18; uric acid, 3.5;

creatinin, 1.4; blood sugar, 90; chlorides, 480 mgm. per 100 cc. of whole blood.

On February 16, 1928, gall bladder not visualized by Graham technique.

On February 27, 1928, blood sugar 75 and blood chlorids 360 mgm. per 100 cc. of whole blood.

On March 1, 1928, death occurred. Autopsy report. Liver weighed 2790 grams. Surface irregularly lobulated and covered with plastic exudate. There are several superficial areas of gray, lobulated, umbilicated infiltration resembling carcinomatous metastases. Hemorrhagic chocolate-colored pus escaped from sinus. Section through the greatly enlarged right lobe reveals a necrotic cavity about the size of a grapefruit, and smaller adjacent cavities communicate with the larger one. Section through liver substance reveals circumscribed gray nodules of variable size. The left lobe is uninvolved. Gall bladder is moderately distended with tarry bile. The common duct, cystic duct, and left branch of the hepatic duct are all patent and unobstructed. The right branch of the hepatic duct is lost in the wall of the necrotic area, and continuity and patency cannot be determined. Both pressure and necrosis of tributaries seem probable.

This case again illustrates the cause of the direct reaction obtained by the van den Bergh test and explains the 20 per cent dye retention. On February 27, 1928, it is to be noted that blood sugar was 75 and chlorids 360 mgm. per 100 cc. of whole blood were obtained and on this date tetany and coma developed, death occurring March 1, 1928.

CASE IV (see Figs. 5 and 6).—Obstruction by stone in the ampulla. Increasing jaundice requiring operation. 'Operative failure indicated by van den Bergh test. Change in laboratory findings after drainage was established. Continued improvement after (external) drainage ceased.

A man (No. 27688), aged fifty-three years, with an acute attack of pain in right upper quadrant, followed by jaundice. He had had two paralytic strokes with good recovery. He was a chronic alcoholic. Gall bladder was not visualized by the Graham technique.

On December 21, 1927, van den Bergh direct immediate reaction, quantitative findings, 8.7 mgm. per 100 cc.; icterus index, 225.

On December 22, 1927, the bilirubin quantitative estimation was 9.75 per 100 cc.

On December 28, 1927, bromsulphalein test showed 95 per cent retention at the end of five minutes and 85 per cent at the end of thirty minutes. No dye recovered from duodenum.

On December 31, 1927, van den Bergh direct immediate with a quantitative finding of 8.5 mgm. per 100 cc.; icterus index, 245; blood chemistry, N.P.N., 41; urea nitrogen, 28; uric acid, 4.6; creatinin, 1.9; blood sugar, 94; chlorids, 40 mgm. per 100 cc. of whole blood.

On January 1, 1928, urine contains bile, stools and duodenal contents negative for bile.

On January 3, 1928, van den Bergh quantitative 8.7 mgm. per 100 cc. Urine shows numerous casts and a heavy trace of albumin. Operation this date. Gall bladder found filled with stones; common duct distended and blocked by a stone in the ampulla. Gall bladder cleared of all stones and drained. Stone in ampulla dislodged and felt to pass down the duodenum. The common duct and duodenum not opened. The operation was hurried, because of anesthetic difficulties requiring artificial respiration.

On January 4, 1928, no drainage from gall bladder. Van den Bergh quantitative findings 7.8 mgm. per 100 cc.

On January 5, 1928, no drainage from gall bladder. Only 125 cc. of urine obtained in forty-eight hours since operation. Van den Bergh direct immediate reaction, quantitative findings, 11; blood chemistry, N.P.N.,

129; urea nitrogen, 113; uric acid, 10; creatinin, 4.5; blood sugar, 127; chlorids, 410 mgm. per 100 cc. of whole blood.

On January 7, 1928, following manipulation of the drainage tube, a large stone escaped and free drainage of bile was established. Blood transfusion, citrate method, 500 cc.

On January 9, 1928, van den Bergh direct immediate reaction, quantitative findings, 3.9 Blood chemistry, N.P.N., 139; urea nitrogen, 115; uric acid, 10; creatinin, 4.5; blood sugar, 75; chlorids, 330 mgm. per 100 cc. of whole blood.

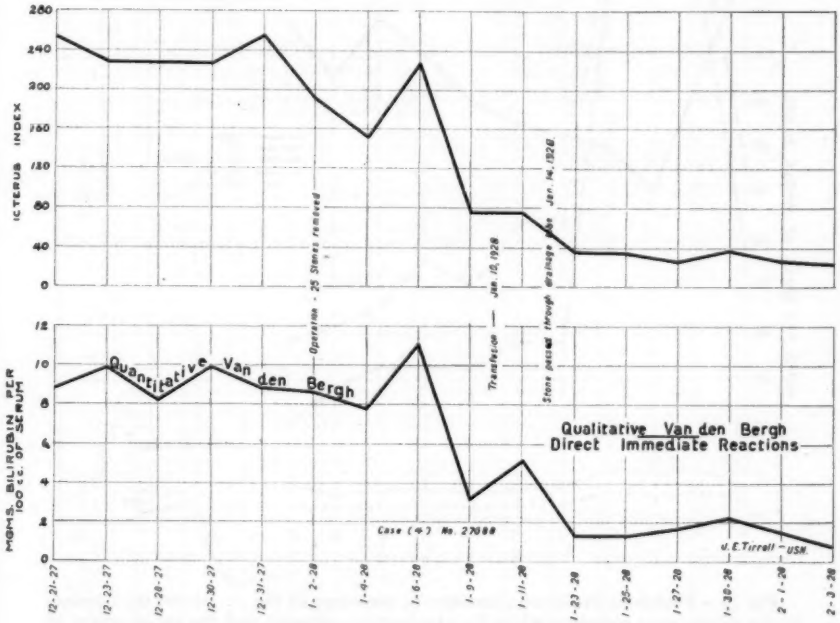

FIG. 5.—Obstruction by stone in common duct. The van den Bergh curve indicates incomplete obstruction. On January 6 the van den Bergh reaction indicated failure to relieve obstruction by operation. After free drainage was established the serum bilirubin fell to normal. Note how the icterus index parallels the van den Bergh curve.

On January 10, 1928, no improvement. Transfused. Note: patient exhibited symptoms of tetany and was in coma. Glucose and sodium chlorid given in sufficient quantity to raise these substances to their normal level.

On January 16, 1928, condition excellent. Blood chemistry, N.P.N., 64; urea nitrogen, 37; uric acid, 5.5; creatinin, 1.7; blood sugar, 107; blood chlorids, 500 mgm. per 100 cc. of whole blood.

On January 23, 1928, up and about. Drainage from the wound has ceased. Van den Bergh normal limits. Blood chemistry, N.P.N., 64; urea nitrogen, 37; uric acid, 4.6; creatinin, 1.5; blood sugar, 84; chlorids, 510 mgm. per 100 cc. of whole blood.

On January 25, 1928, van den Bergh normal. Blood chemistry, N.P.N., 50; urea nitrogen, 37; uric acid, 4.6; creatinin, 1.2; blood sugar, 90; chlorids, 510 mgm. per 100 cc. of whole blood. On this night, the patient went

ashore and ate a big meal of pig's feet, sauerkraut and mince pie with plenty of beer and strong alcoholics. He experienced no discomfort whatever from this orgy.

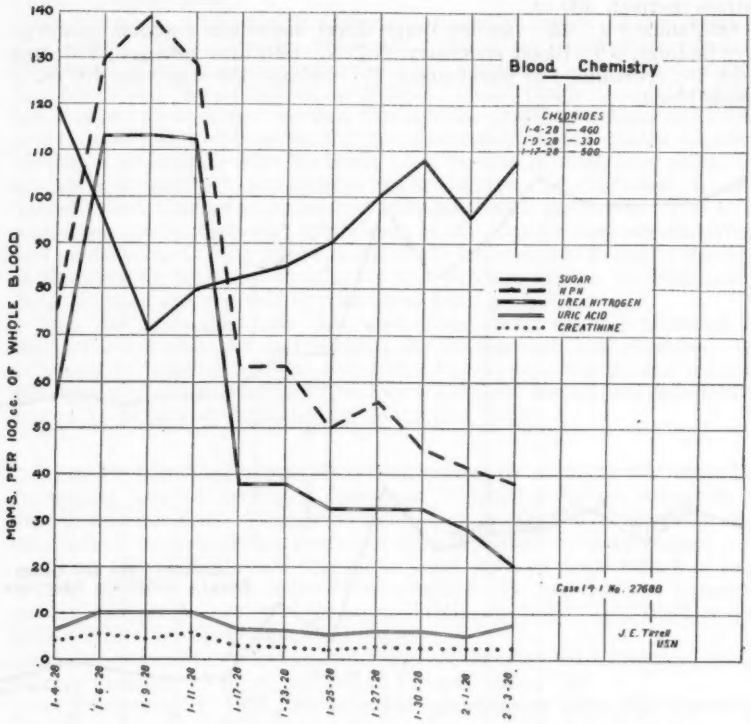

FIG. 6.—Postoperative blood chemistry in same case as Fig. 5. Shows the increase in the nitrogenous elements while the obstruction persisted and the rapid return to normal after the obstruction was relieved. This case illustrates the manner in which the laboratory can prove the success or failure of the operation. Note that, on January 9, with low chlorids and sugar, coma and tetany developed. Transfusion with intravenous chlorids and sugar relieved these symptoms.

This was one of the most difficult and interesting cases we have had for a long time, presenting many problems of diagnosis, operative procedure and postoperative treatment, the details of which are not germane to this paper. Evidently the blocking of the duct was not complete, for the laboratory reports indicated slight leakage, but at no time could dye or bile be obtained by duodenal siphonage. The gall bladder was left in because it appeared probable that it might be required for anastomosis to the stomach or duodenum if the common duct inflammation persisted. The common duct was not drained because of the anesthetic crisis. We do not know whether the continued blocking of the common duct after operation

was due to another stone or to inflammation, but it became patent after drainage through the tube in the gall bladder was established. Colp's article contains an excellent discussion of the common errors in operation that lead to these difficulties. The laboratory tests were of great help in determining whether or not it was safe to discontinue drainage, they also gave valuable aid in indicating proper postoperative treatment.

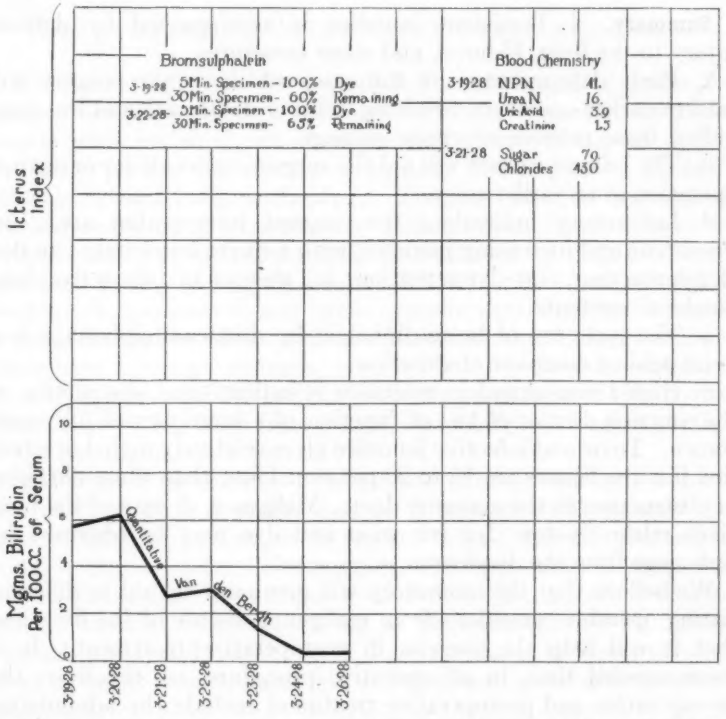

FIG. 7.—Illustrating the van den Bergh curve and bromsulphalein dye retention in a case of occlusion of the common duct by stone, with relief upon passage of stone

CASE V (see Fig. 7).—Obstruction by stone in common duct. Rapid recovery after spontaneous relief of obstruction.

A man (No. 25862), aged fifty-six years. One year ago had sharp epigastric pain with nausea and vomiting, chills, followed by jaundice. Four months ago had exploratory operation, at which time nothing pathologic was found on careful examination of the gall bladder and ducts. During convalescence, he had another attack of acute abdominal pain with nausea, vomiting and chill followed by jaundice.

March 18, 1928. Admitted with acute abdominal pain, nausea and vomiting, chill, later was jaundiced.

March 19, 1928. Dye retention 100 per cent at five minutes, 65 per cent at thirty minutes; van den Bergh reaction direct immediate, 5.8 mgm.

100 cc. of blood, icterus index, 56. Blood chemistry, N.P.N., 41, urea nitrogen, 16; uric acid, 2.9; creatinin, 1.5; sugar, 115; chlorids, 530.

March 20, 1928. Comatose. Van den Bergh, 6.4, chlorids, 345; sugar 68 mgm. per 100 cc. of blood.

On March 21, 1928. Much better. Van den Bergh, 2.8. Blood chemistry, sugar, 79; chlorids, 430.

March 22, 1928. Jaundice much less, free from symptoms. Van den Bergh, 3; dye retention 100 per cent at 5 minutes, 65 per cent at thirty minutes.

Summary. 1. Persistent jaundice is accompanied by definite injury to the liver, kidneys, and other structures.

2. Early determination of the cases which require surgery will lead to earlier operation, resulting in lower death rate and less morbidity from permanent tissue damage.

3. The laboratory test will aid the surgeon to decide for or against operation at an earlier stage.

4. Laboratory indications for surgical intervention are: (*a*) Persistent and increasing jaundice, with a direct immediate van den Bergh reaction; (*b*) dye retention; (*c*) absence of bile or dye from duodenal contents.

5. The recovery of bromsulphalein by duodenal siphonage is a point against complete obstruction.

6. High bromsulphalein retention is indicative of obstruction of the common duct or of loss of function of a large part of liver substance. Toxic and infective jaundice gives relatively high dye retention but the figures are 15 to 20 per cent lower than those obtained in obstruction to the common duct. Malignant disease of the liver gives relatively low dye retention and dye may be obtained by siphonage from the duodenum.

We believe that the laboratory will give material aid in differentiating operable conditions from malignant disease of the liver and that it will help the surgeon in postoperative treatment. It is recommended that, in all operative procedures on the liver, the pre-operative and postoperative treatment include the administration of glucose and sodium chlorid. It has been shown that cholemia and tetany may be controlled by the adequate administration of these substances.

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THE EFFECT OF IODIN UPON EXPERIMENTAL HYPERTHYROIDISM IN MAN.

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Although iodin has been used in the treatment of goiter for many years, at least since 1820 when Coindet[1] reported successful results with the drug, its employment fell into disrepute during the latter part of the nineteenth century due largely to Kocher's attitude toward iodin medication. The first detailed accounts of its therapeutic effect were made by Neisser,[2] who reported upon the "microdosage" of potassium iodid in 1920 and by Plummer,[3] who described the use of Lugol's solution in 1923. Since then, there has been much speculation and some experimental work with regard to the mechanism of its action. Rienhoff[4] convincingly demonstrated the histologic changes brought about by the administration of iodin in exophthalmic goiter by resecting a portion of the thyroid gland, then giving iodin for a period, and finally resecting a portion of the remainder of the gland.

Hildebrandt[5] produced a hyperthyroid state in rats by the injection of thyroxin. A single dose of potassium iodid reduced the basal metabolism in a single rat from +15 to +4, but had no effect in two other animals. Furthermore, the hyperthyroid state was not maintained at a constant level before giving iodid. Sturgis and his associates[6] injected 1 mg. of thyroxin into rabbits intravenously and found that 0.1 cc. of Lugol's solution had no protective effect as far as weight, pulse rate and the basal metabolic rate were concerned.

Blalock and Harrison[7] produced a hyperthyroid state in dogs previously thyroidectomized by feeding thyroid extract. They concluded that the administration of iodin reduced the basal metabolic rate, the decrease lasting six to ten days, after which the metabolism rapidly increased. Their work is not entirely convincing however. Their three animals all gained 30 per cent in weight during the experiment, which is contrary to the usual course of hyperthyroidism. In the case of dog VI6 the dose of thyroid extract was reduced from 0.7 gm. to 0.4 gm. when iodin was given. (It will be seen from one of our experiments that reducing the dosage of thyroid when giving iodin may result in a fall in metabolism which is *not* due to iodin.) With dog VI8 the metabolism fell from +89 to +80 in sixteen days before iodin was given. With iodin it rose to

+97 in five days, and then fell to +71 in four days. Three weeks after all medication was stopped the rate was +139.

More recently Kunde[8] has shown that Lugol's solution is ineffective in reducing metabolism in dogs rendered hyperthyroid by the ingestion of thyroid substance and that it fails to protect the animal against an increase in metabolism when administered simultaneously with thyroid. Martin[9] has reported a fall in the metabolism of patients suffering from pernicious anemia and the afebrile stage of acute rheumatic fever following the exhibition of iodin. Cushing and Davidoff[10] have described a similar result in one of a few cases of acromegaly. In the normal human being iodin has no such effect according to Martin (*loc. cit.*) and Liebesney.[11] According to the latter, on the contrary, metabolism tends to rise.

The evidence at hand from experimental hyperthyroidism in animals, then, is confusing, and the fact that iodin can reduce metabolism in rheumatic fever, acromegaly and pernicious anemia, diseases in which the drug is not a particularly successful therapeutic agent, makes the question all the more complicated. It, therefore seemed desirable to us to observe the effects of iodin in experimental hyperthyroidism in man.

Experimental. The equivalent of a hyperthyroid state without goiter was produced in 4 individuals by ingestion of thyroid extract. One subject was a medical student who volunteered to take part in the experiment. Another was a hospital patient who consented to take thyroid extract, although he was told that elevating his low basal metabolic rate might have no effect at all upon the sluggish ulcer of his skin and fascia. The authors were the other subjects. Iodin was given in the form of Lugol's solution because its use has become a custom in the profession and not because there is any particular virtue in this compound. Observations were made on the pulse rate, basal metabolic rate and symptoms.

Case Reports. CASE I. (See Chart I.)—Subject I was a man aged sixty-three years, with an arteriosclerotic ulcer of the leg requiring rest in bed in hospital. The initial pulse rate was 68; B.M.R. −22. On daily doses of 0.2, then 0.4, and then 0.6 gm. of thyroid extract (Armour) the B.M.R. reached −2. On the eighteenth day, the basal rate was +33; pulse, 92. Meanwhile, the subject complained of nervousness, loss of appetite, sweating and insomnia. It did not seem justified to keep him in this condition so the dose was reduced to 0.4 gm. a day with a fall in basal rate to +19 on the twenty-first day. Unfortunately he was not observed for a longer period at this dosage but was immediately given iodin, 1 cc. of Lugol's solution twice a day. The pulse rate was quite irregular but chanced to be 78 on the twenty-eighth day when iodin was stopped.. The basal rate fell to +2 on the twenty-fourth day and was +6 on the twenty-eighth. He was then kept on the same dose of thyroid, 0.4 gm., but without iodin. The metabolism rose to +19 on the thirty-first day and fell to +10 on the thirty-seventh. The pulse continued to be rapid, 84 to 96; there was no relief from symptoms during iodin medication. Thyroid was stopped on the thirty-seventh day with gradual relief of symptoms and fall in pulse to a

normal rate over a period of two weeks. No further determinations of the basal metabolism were made.

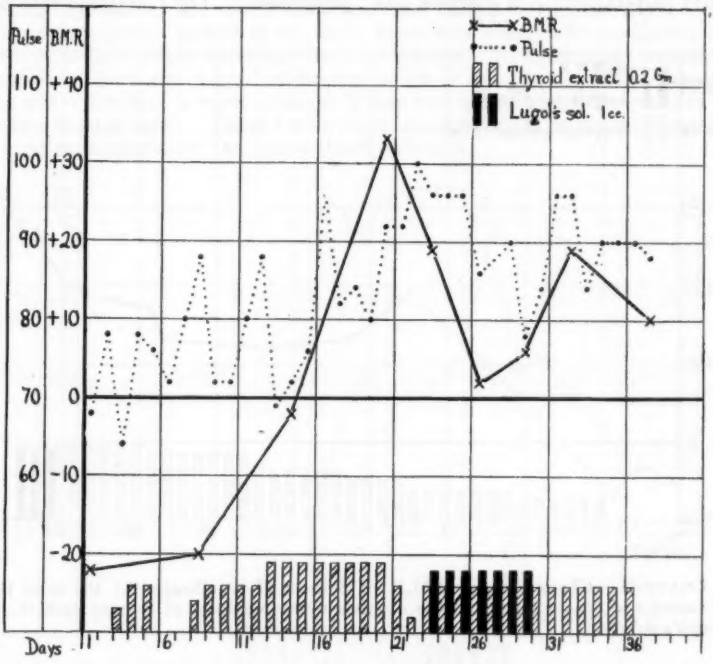

CHART I.—Changes in the pulse rate and B.M.R. of Subject I are indicated by the dotted and solid lines. Hatched and blocked areas in the abscissa represent doses of thyroid extract and Lugol's solution.

CASE II. (See Chart II.)—Subject II was a healthy man aged twenty-nine years, who carried on his usual work as an officer of the medical school throughout the experiment. A careful record of his pulse rate was not kept. The initial metabolic rate was −5, −3, and −7 on three days over a period of ten days. He then took thyroid extract (Burroughs and Wellcome) 0.6 gm. for six days, 1 gm. for seven days, 1.3 gm. for four days, 1.6 gm. for five days, 2 gm. for one day, 2.3 gm. for seven days, and finally 2.6 gm. for five days. The metabolic rate rose gradually to a level around +19 during this period. The first onset of symptoms came on the fifteenth day of thyroid ingestion when he was suddenly taken with tachycardia, palpitation, breathlessness and nausea while climbing a steep mountain. Thereafter he had a rapid pulse upon the slightest exertion, although his basal morning pulse was slow; extreme fatigue, sleepiness and increased appetite. Beginning with the thirty-sixth day he took 9 drops of Lugol's solution a day for three days, continuing with thyroid extract at 2.6 gm. per day. He noticed no amelioration of symptoms and stopped the experiment after finding that his basal rate was +29 on the thirty-ninth day.

CASE III. (See Chart III.)—The third subject was a healthy man aged thirty-one years, who carried out his duties as a hospital house officer throughout the experiment. The initial basal metabolic rate was +4; pulse

rate 66. On 0.3 gm. of thyroid extract (Armour) there was practically no change over a period of eight days. Taking 0.6 gm. daily there was a gradual increase in pulse rate, sensation of fullness in the head, fatigue, mild palpitation upon exertion and "jumpiness." The metabolic rate was

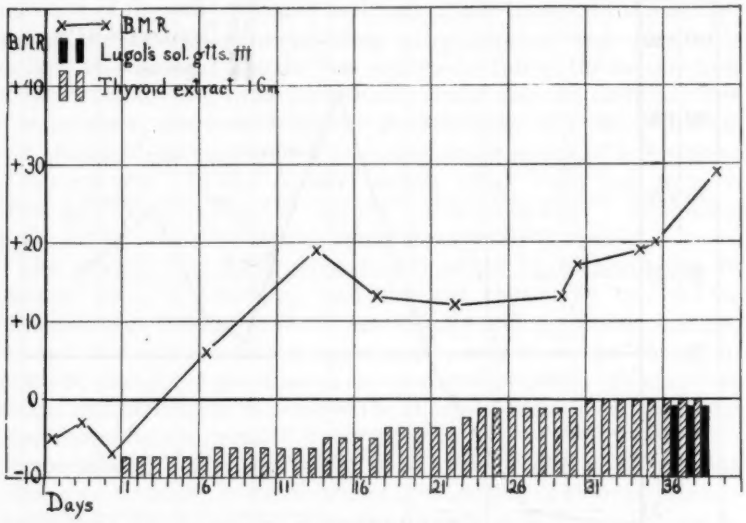

CHART II.—Change in the B.M.R. of Subject II is indicated by the solid line. Hatched and blocked areas in the abscissa represent doses of thyroid extract and Lugol's solution.

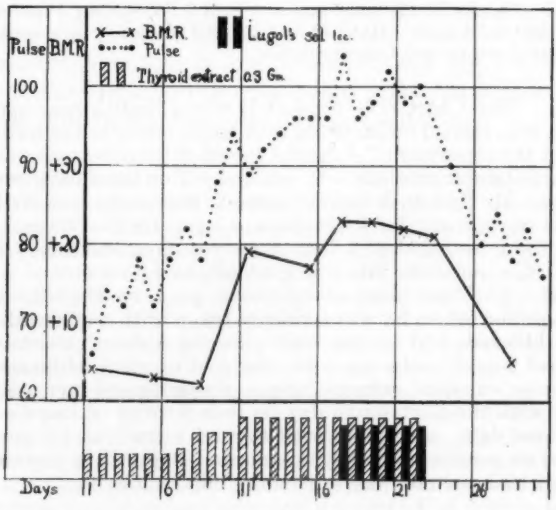

CHART III.—Changes in the pulse rate and B.M.R. of Subject III are indicated by the dotted and solid lines. Hatched and blocked areas in the abscissa represent doses of thyroid extract and Lugol's solution.

+19 on the eleventh day. He then took 0.8 gm. for six days, during which period the metabolic rate rose to +23 and he noticed tachycardia, palpitation, anorexia, excessive fatigue, breathlessness, and a slight tremor. Continuing thyroid extract at the same dose and taking Lugol's solution, 1 cc. twice a day over a period of six days, there was practically no change in the metabolic rate nor any relief from symptoms. All medication was then stopped. There was a gradual improvement in symptoms; the metabolic rate was +5 within a week although it was two weeks before the pulse rate became normal again. Three weeks after the experiment ended he was able to indulge in strenuous exercise without difficulty.

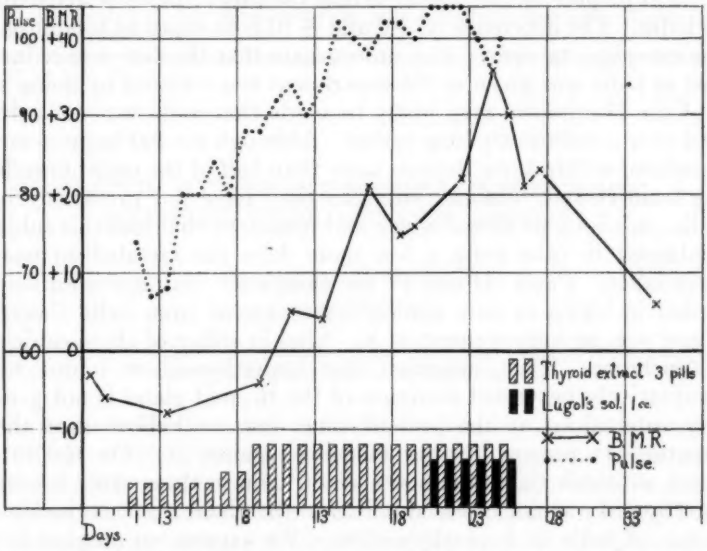

CHART IV.—Changes in the pulse rate and B.M.R. of Subject IV are indicated by the dotted and solid lines. Hatched and blocked areas in the abscissa represent doses of thyroid extract and Lugol's solution.

CASE IV. (See Chart IV.)—The fourth subject was a healthy man, aged twenty-six years, who continued his work as a medical student throughout the experiment. The initial basal metabolic rate was −3 to −6; pulse rate 74. He took 6 pills of a Danish thyroid preparation* for six days, 9 pills for two days, and then 16 pills for eleven days. The basal rate was +15 on the eighteenth day; +16 on the nineteenth. During this period he became easily fatigued, lost his appetite, and noticed palpitation, tachycardia, nervousness and increased perspiration. There was a slight tremor; he lost about 4 pounds in weight. On the twentieth day he commenced taking 1 cc. of Lugol's solution twice a day, continuing the thyroid as before. After six days of this, the basal rate was +30, the pulse rate unchanged and his symptoms were not in the least ameliorated. Unfortunately he developed an acute coryza in the last three days of the experiment which undoubtedly resulted in a false high level of metabolism (+36 on the twenty-fourth day), for with disappearance of his cold the rate was +23 two days

* A preparation made by the Danish Medical Company, Copenhagen, and standardized by its power to cause metamorphosis in the tadpole. Each pill represents 200 hormone units.

after the experiment ended. His symptoms were rapidly relieved, a week later the basal rate was +6, and he had recovered the loss of weight in ten days.

Discussion. All four subjects went through a mild hyperthyroidism as it is commonly seen in the human, without goiter and exophthalmos. Although there was an apparent fall in metabolism in Subject I following the exhibition of iodin, subsequent observations showed that 0.4 gm. of extract was not sufficient to maintain metabolism at its previous high level so that the effect cannot be attributed to iodin. The difference of +6 and +10 is so small as to approach the experimental error. It is unfortunate that the dose was reduced just as iodin was given as the experiment was vitiated by doing so. In Case II criticism may justly be made that iodin was not exhibited over a sufficiently long period. Although clinical improvement is noticed within three days in more than half of the patients suffering from Graves' disease, provided they have not previously had iodin, this is by no means a rule and it may be that had this subject continued to take iodin a few more days the metabolism would have fallen. Cases III and IV are clean cut. Six days is an ample period in which to note clinical improvement from iodin therapy. There was no improvement of any kind in either of these subjects.

Conclusion. The conception that hyperthyroidism is due to a qualitatively perverted secretion of the thyroid gland is not generally entertained at the present time, but we believe that these experiments present further evidence against it. On the other hand, we think that the impotence of iodin in these cases in which the thyroid was not diseased points to the gland itself as the site of action of iodin in hyperthyroidism. We express no opinion as to whether its effect is a mechanical blockage of absorption as conceived by Marine[12] or a change in the intracellular metabolism.

Summary. 1. A state of artificial hyperthyroidism was produced in four adult males by the ingestion of thyroid extract.

2. Iodin had no effect upon this pathologic condition.

3. The results suggest that the therapeutic effect of iodin in hyperthyroidism is produced by its action on the thyroid epithelium.

NOTE.—It is a pleasure to acknowledge our thanks to Mr. David Brinkerhoff, who served as a subject in these experiments.

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INSULIN HYPERSENSITIVENESS: IMMUNOLOGIC CONSIDERATIONS AND CASE REPORTS.*

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Ever since the discovery of insulin by Banting and his coworkers in 1922, considerable attention has centered upon its characteristics and clinical application. As a result, a very considerable literature has accumulated, a large portion of which has concerned itself with the possible untoward effects resulting from its administration, referring particularly to the hypoglycemic reaction. This reaction, it has been shown, results from a marked and rapid lowering of blood sugar to a subnormal level, brought about through the hormone action of insulin. Recent chemical studies by Abel,[1] Schonle and Waldo[2] and others have shown that the insulin as prepared from either beef or pork pancreas is either a protein or complex proteose and contains even after purification and recrystallization, an average of 0.006 to 0.01 mg. nitrogen per unit. This amount of protein is so small that in the average case the possibility of inducing hypersensitiveness because of repeated administration is unlikely and reports of such instances in the literature consequently are rare.

In the early period of insulin administration before adequate methods of purification and concentration had been introduced, reactions of hypersensitiveness described as anaphylactic were not infrequently reported. Thus, in 1922 in a series of clinical articles on insulin, such reactions are mentioned as occurring in 2 patients

* Read before the Cosmopolitan Medical Club, March 16, and the Section on General Medicine, College of Physicians of Philadelphia, March 26, 1928.

by Williams,[3] 3 by Wilder,[4] 4 by Joslin[5] and in 3 by Geyelin.[6] Abroad, record of similar untoward reactions is to be found in case reports by Lereboullet[7] *et al.*, in July, 1924, Raymond and La Croix[8] in May, 1925, and by Achard and Bloch[9] in July, 1925. In all these instances the reactions followed the injection of from 5 to 15 cc. of the early unpurified form of insulin containing fairly large amounts of protein and were usually in the nature of a mild serum sickness. No mention is made in most of these instances as to whether the reaction followed the initial insulin injection or a later one. In the case reported by Raymond and La Croix the reaction occurred on the fifty-fifth day of insulin treatment, previous injections apparently having no untoward effect; in this instance, symptoms followed ten minutes after the injection of 5 cc. insulin and consisted of retrosternal constriction, edema of the face and urticaria. On account of the recurrence of these symptoms following a similar injection given the next day, further insulin treatment was discontinued. Nine months later a reinjection of only $\frac{1}{4}$ cc. of insulin was followed by redness of face and edema of the lids, this recurring daily after each injection. On the seventh day a similar injection was followed by giant urticaria, edema of the tongue and edema of all the injection sites, pruritus and symptoms of vasomotor collapse, these symptoms persisting for two hours. Skin tests for insulin sensitivity in this patient were found to be strongly positive.

Such reactions were obviously due to the relatively large amount of protein contained in the earlier insulin preparations but with the introduction of more satisfactory methods of purification and concentration, Campbell,[10] in 1924, in summarizing the clinical aspects of insulin, mentions that only an occasional urticarial reaction was observed. Since this time record of only 2 additional cases could be found in the literature, 1 by Walker[12] in July, 1927, and another by Engelberg[11] in February, 1927. In Walker's patient a small dose (12 units) of the more purified insulin being used at this time given on the sixth day of insulin treatment, was followed by generalized urticaria and edema, recurring on the following day after similar injection. Change in dosage and time of administration of insulin obviated further reactions. In the patient reported by Engelberg urticaria and collapse followed injection of 20 units of Welcome's insulin; here too change in dosage and site of administration obviated further difficulty.

In all these case reports there is little or no mention as to the nature of these reactions and except for the occasional demonstration of cutaneous sensitivity to insulin, no other attempt was made to study their immunologic character. Most of these reactions were assumed to be due to a sensitization to either beef or pork protein, depending upon which kind of pancreas was used, and change from one preparation to another usually obviated further difficulty. Occasionally, however, as mentioned by Campbell, some cases would

continue to show sensitization even when the purest form of insulin was used. Such cases, he believed, would not respond to change in insulin preparation and would require desensitization methods as applied in Geyelin's cases.

Recently, a similar reaction of hypersensitiveness to insulin occurred in a patient under the care of the writer, offering an unusual opportunity for carrying out a series of immunologic studies of a character not previously recorded in the literature. The results of these studies have proven of sufficient interest and importance to warrant their report.

Case Reports.—CASE I.—The patient, Mrs. D. S., aged sixty-two years, was first seen in September, 1926, and was found at this time to have a mild diabetes mellitus with an accompanying arteriosclerosis. In April, 1926, because of a progressive diabetic gangrene, a high amputation had been done at the Mt. Sinai Hospital. While in the hospital for a period of two weeks prior to her operation and four weeks subsequent to it, the patient received daily injections of insulin in doses of 10 units and only on one occasion was any untoward reaction noticed after these injections. On this occasion, occurring two weeks after the operation, following an injection of insulin into the arm there was marked induration and swelling lasting about two weeks but no general reaction. Subsequent injections given in other portions of the body produced no similar reaction.

Following her discharge from the hospital, the patient was kept on a maintenance diet without insulin and maintained a normal blood sugar for a period of sixteen months. On October 16, 1927, the patient developed an acute pyelonephritis, causing a marked hyperglycemia and mild acidosis with considerable vomiting not relieved by medication. To control this, on October 20, she was given a high-carbohydrate diet and insulin, the first dose being 10 units before breakfast. On October 22, this was increased to 10 units morning and evening; on October 25 to 20 units in the morning and 10 units in the evening and on October 27, 20 units in the morning and 15 units in the evening. Except for the slight transitory stinging effect of the insulin, no local reaction followed any of these injections, and the general condition except for a mild hyperglycemia seemed to improve. On October 30, as the patient began to eat her breakfast and 15 minutes following the injection of 20 units of insulin (U40 Lilly), she suddenly began to feel weak, was nauseated and vomited. At the same time, an urticarial rash, extremely itchy in character, appeared rapidly on her face, neck, arm and body, the wheals being discrete at first but later coalescing. This rash disappeared at the end of an hour, and except for slight weakness the patient's general condition remained good. Because of this reaction, the insulin dosage was reduced to 10 units in the evening and 15 units in the morning. Before the evening meal of the same day 10 units of U20 insulin Lilly was given, and except for slight local pain no other untoward reaction occurred. On the following morning, 15 units of the U20 insulin Lilly was given and fifteen minutes later the patient again had a similar recurrence of the generalized urticaria, with intense itching and marked swelling of the arms, hands and left leg, the edema of the hands persisting two to three days and that of the leg about two weeks.

Blood taken just prior to insulin administration was found to contain 260 mg. of sugar. The patient refused further insulin administration and since her vomiting had ceased and her renal function was at this time greatly improved, the diet was changed back to her original maintenance diet, upon which she has been able to maintain a normal blood sugar until the present

time. Subsequent to the occurrence of the reaction, detailed inquiry into the patients past and family history failed to reveal any evidence of other forms of human hypersensitiveness having occurred in either the patient or her family.

The unusual character of the reaction, with on two occasions an urticarial eruption appearing ten to fifteen minutes after an injection of insulin together with a preliminary blood-sugar reading of 260 mg., indicated that the reaction in this instance was one of hypersensitiveness rather than of hypoglycemia. This contention was further strengthened by the results of skin tests carried out on the patient shortly after the occurrence of the reaction. About 0.02 cc. of each of the two insulin preparations used by the patient prior to the reaction, viz., U20 Lilly and U40 Lilly, were injected into

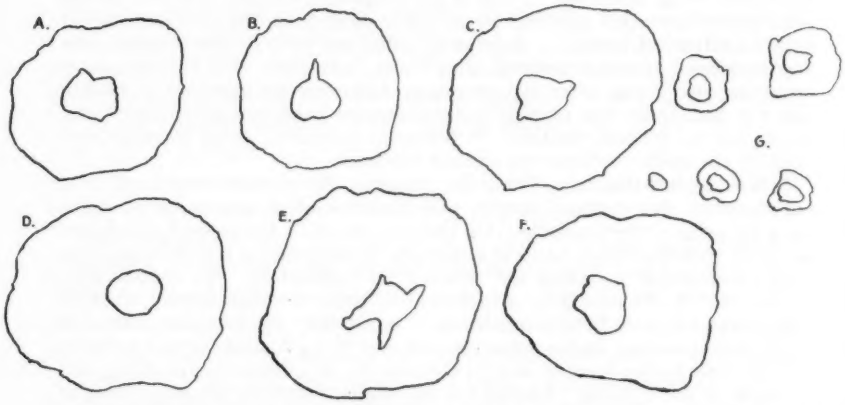

FIG. 1.—Skin tests on patient D. S. with various preparations of insulin. *A*, Insulin—Lilly U40 (original); *B*, insulin—Lilly U20 (original); *C*, insulin—Mulford U40; *D*, insulin—Mulford U20; *E*, insulin—Lilly U40 (different lot); *F*, insulin—Stearns U40; *G*, insulin—Lilly U40 on normal and diabetic patients (types of reaction in control cases).

the arm intradermally. Within ten minutes a large urticarial wheal with pseudopods and a fairly large surrounding zone of erythema resulted in each instance. Similar tests with other commercial preparations of insulin as Mulford's U20 and U40, Stearn's U40; Lilly's U40 specially prepared from a mixture of beef and pork pancreas and one prepared from beef pancreas alone,* all gave similar marked reactions (Fig. 1 and 2). Finally, similar testing with a solution of purified recrystallized insulin obtained through the courtesy of Dr. J. J. Abel and prepared according to his directions so as to give a concentration of approximately 40 units per cc. also gave a marked reaction. Simultaneously skin tests with the diluting

* Obtained through the courtesy of Eli Lilly & Co.

fluid used in dissolving the insulin proved negative. As a contrast, similar skin tests carried out both with the commercial insulin preparations and that prepared by Abel on 10 diabetic patients not receiving insulin, 10 diabetic patients receiving varying amounts of insulin and 20 normal individuals showed in all instances negative reactions. It would seem from these observations that there was present in our patient a distinct cutaneous sensitivity to insulin protein itself. As a corollary to this opinion, skin tests with extracts of beef and pork protein prepared by the method described by Coca[13] were negative when tested on the patient, whereas similarily prepared extracts of beef pancreas and pork pancreas gave marked reactions identical with those produced by insulin..

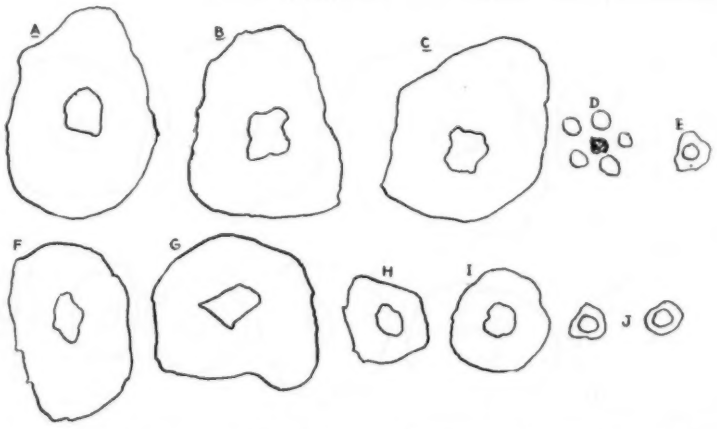

FIG. 2.—Skin tests on patient D. S. *A*, insulin—Lilly U40 (beef and pork pancreas); *B*, insulin—Lilly U40 (beef pancreas alone); *C*, insulin—Abel (purified); *D*, insulin—Abel on normal persons (controls); *E*, insulin—diluting fluid (control); *F*, beef pancreas—extracted with Coca's fluid; *G*, pork pancreas—extracted with Coca's fluid; *H*, beef extract—extracted with Coca's fluid; *I*, pork extract—extracted with Coca's fluid; *J*, cottonseed and Le Page glue extracts.

The degree of cutaneous sensitivity was found to be fairly high, since skin tests with varying concentrations of insulin prepared by diluting the U20 preparation with the insulin diluent gave marked reactions with a concentration of 0.5 unit; a moderate reaction with 0.25 unit and a slight reaction with 0.05 unit (Fig. 3).

In order to determine further the character of this form of hypersensitiveness, the patient's serum was obtained ten days after the recurrence of the reaction and studied for the possible presence of antibodies. Of greatest interest are the results of local passive transfer of the patient's serum to human skin in order to detect in it the presence of specific reacting antibodies or reagins. This method first introduced by Praussnitz and Kustner,[14] in 1921, and confirmed by De Besche[15] in 1923, has recently been extensively

applied by Coca and Grove[16] in the study of a large number of patients with varied forms of human hypersensitiveness. These latter observers have by this method been able to show that in the blood of all so-called atopic individuals—that is individuals with an inherited form of hypersensitiveness such as hay fever and bronchial asthma—there is present specific reacting or sensitizing bodies, corresponding to the antigen or exciting agent to which they are cutaneously sensitive. To these bodies they have applied the term "atopic reagins" in order to distinguish them from anaphylactic antibodies, since these latter apparently present different characteristics. They were not able, however, to detect the presence of similar reagins in the serum of any of the cases of urticaria or drug hypersensitiveness which they are able to study.

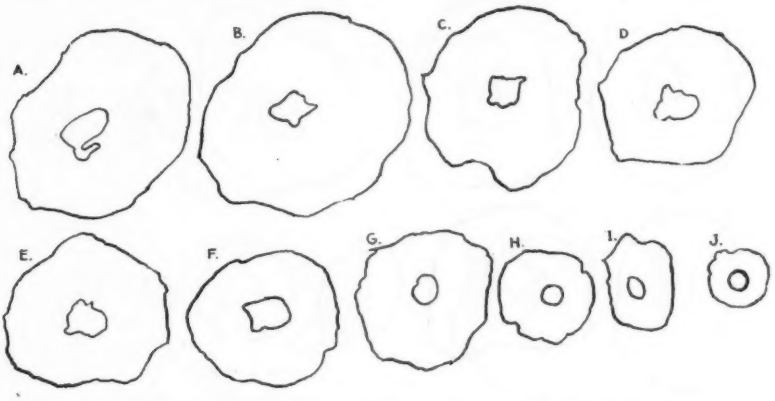

FIG. 3.—Skin tests on patient D. S. with varying concentrations of insulin—Lilly U40. *A*, U40; *B*, U20; *C*, U10; *D*, U5; *E*, U1; *F*, U0.5; *G*, U0.25; *H*, U0.05; *I*, insulin diluting fluid (control); *J*, type of reaction with insulin—Lilly U40 on normal person (control).

The technique of the method of local passive transfer is fairly simple; the patient's serum is passed through a Berkefeld or Zeitz filter and 0.1 cc. of it is injected intradermally into the arm of several normal individuals. Twenty-four hours later, 0.02 cc. of the exciting agent is injected into both the sensitized site and at the same time into an adjacent nonsensitized or control site. If positive, a large wheal with surrounding zone of erythema similar to the patient's original cutaneous reaction should appear within ten minutes in the sensitized site and none in the control site. The above technique was followed in the study of the serum of the patient herein reported, 0.1 cc. was injected into the arms of two normal individuals; twenty-four hours later 0.02 cc. of the various insulin preparations tested on the patient were injected into the sensitized sites with control injections alongside. Within ten minutes in each sensitized site a positive reaction similar in every respect to the reactions obtained

previously in the skin tests on the patient were obtained, whereas the control injections were negative (Fig. 4); twenty-four hours later a reinjection of insulin into these sites failed to produce a reaction, indicating that desensitization of these sites had occurred. Furthermore injections of these sites with an extract of beef protein and one of pork protein failed to produce a reaction. As a contrast injection of beef extract, pork extract, a strong cottonseed extract (0.01 mg.) and one of Le Page glue (0.05 mg.) each into freshly prepared sites failed to bring out a reaction, and forty-eight hours later injection of insulin into these same sites was followed in each instance by a marked reaction similar to that previously described, thus

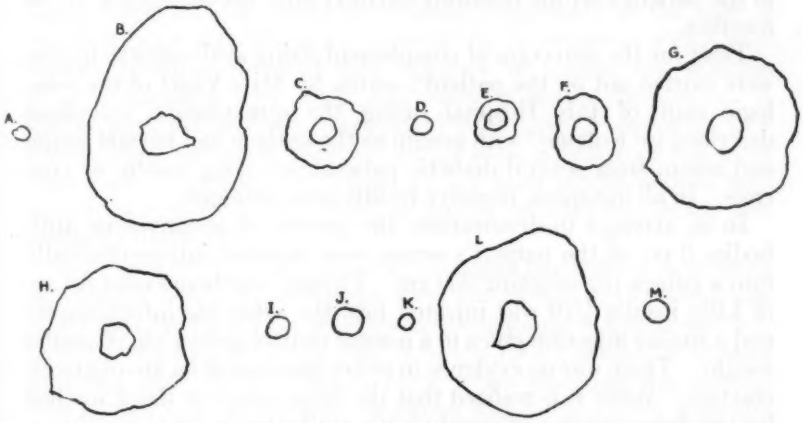

FIG. 4.—Reagin studies with serum of patient D. S. *A*, sensitized site[1] before injection; *B*, sensitized site after injection of insulin—Lilly U40; *C*, nonsensitized site injected with insulin—Lilly (control); *D*, sensitized site[1] injected with insulin twenty-four hours later; *E*, sensitized site[2] injected with beef extract; *F*, nonsensitized site injected with beef extract (control); *G*, sensitized site[2] injected with insulin twenty-four hours later; *H*, sensitized site[3] injected with insulin—Abel; *I*, nonsensitized site injected with insulin—Abel (control); *J*, sensitized site injected with insulin—Lilly—twenty-four hours later; *K*, sensitized site[4] injected with Le Page glue; *L*, sensitized site injected with insulin—Lilly—forty-eight hours later; *M*, nonsensitized site injected with insulin (control).

indicating that the reaction here is not a nonspecific one but is specific for insulin *per se*. One of the sensitized sites was injected with the fluid used to dissolve the crystallized insulin powder with entirely negative results. Twenty-four hours later injection into this site of the purified insulin of Abel was followed by a marked reaction, with negative result in the control. Forty-eight hours later injection of commercial insulin into the same site was not followed by a reaction, indicating that the antibody or reagin which was present reacted with insulin protein whether in purified form or contained in a commercial preparation.

Search for the presence of other antibodies in the patient's serum

was also made. Attempts to detect precipitins were at first unsuccessful because it was found that when commercial insulin is brought into contact with normal serum a marked precipitation occurs, confirming in this respect similar observations by Ornstein and Mera[17] who because of this precipitation were unable to demonstrate precipitin formation in rabbits as a result of repeated insulin injection. By substituting the purified insulin of Abel and using the capillary-tube method for carrying out the test, it was possible to obtain at the point of contact, a definite precipitation ring with dilutions of insulin as high as 1 to 3000, whereas with normal sera, only a faint ring occurred which disappeared at a dilution of 1 to 100. These results indicate apparently the presence of precipitins against insulin in the patient's serum, obtained ten days after the occurrence of the reaction.

Tests for the detection of complement-fixing antibodies to insulin were carried out on the patient's serum by Miss Yagel of the serologic staff of this Hospital, using the quantitative technique described by Kolmer[18] with insulin as the antigen and normal serum and serum from several diabetic patients receiving insulin as controls. In all instances, negative results were obtained.

In an attempt to demonstrate the present of anaphylactic antibodies 3 cc. of the patient's serum were injected intraperitoneally into a guinea pig weighing 250 gm. Twenty-four hours later 0.1 cc. of Lilly insulin U40 was injected into the same pig intravenously and a similar injection given to a normal control guinea pig of similar weight. There was no evidence in either instance of an anaphylactic reaction. While it is realized that the intravenous or shock method for the demonstration of anaphylactic antibodies is not as conclusive as uterine-muscle-strip method of Dale, nevertheless, the absence of shock coupled with the general nature of the patient's reaction and the presence of reagins make it rather unlikely that anaphylactic antibodies were present in this serum.

Sera of the patient obtained five weeks, ten weeks and four months after the occurrence of the reaction were studied in like fashion for antibodies. In none of these could precipitins be demonstrated, whereas reagins were found present in the fifth week and tenth week specimens and absent in the serum obtained four months after the reaction. All other antibodies including precipitins were absent in all of these sera. These results indicate that precipitins and reagins are present in the serum of the patient, shortly after the occurrence of the reaction, the precipitins disappearing within a short time, while the reagins persist for at least two or three months. Although antibodies were absent at the end of four months, cutaneous sensitivity as determined by skin tests was still found to be present at this time.

Local Hypersensitiveness to Insulin. We have thus far been concerned with a consideration of hypersensitiveness to insulin causing

general manifestations. The occurrence of local reactions to insulin is also recorded in the literature and has been particularly well summarized by Lawrence[19] in 1924. As with general reactions, local reactions were also more frequent with the earlier insulin preparations and at times local sterile abscesses even followed their injection. With increasing purification and concentration, the frequency of these local reactions lessened proportionately, but occasionally even with the purest varieties, marked local reactions occurred in sensitive individuals. Change in the site of injection or the make of insulin seemed more apt to produce local reactions, as noted in 2 cases reported by Lawrence and in each instance injection with the original insulin preparation obviated further local reactions. At times, however, local reactions followed irrespective of the type of insulin used, as in a third case reported by Lawrence in which hard brawny swellings followed each injection of insulin, the reaction being accompanied by fever and swelling lasting two days. A similar local reaction was reported by Sturtevant,[20] occurring in a woman aged sixty-five years, in whom each injection of not more than 1 cc. of insulin was followed by a hard tender nodule with superficial erythema, the reaction lasting seventy-two hours and gradually disappearing.

At the end of six weeks, the reaction began to diminish in severity and within a few days became so slight as not to be annoying. Sturtevant attributed the reaction in this instance to a local anaphylaxis, the appearance being similar to the local reaction sometimes occurring after the injection of horse serum in susceptible persons with no infection, necrosis or sloughing and ceasing after a certain period as though desensitization has occurred. This type of reaction was believed by Lereboullet[7] to be analogous to the necrosis or Arthus phenomenon occurring in the skin of a sensitized rabbit after injection of the offending antigen but the exact mechanism is not known.

Through the courtesy of Dr. Russell Richardson of the Diabetic Clinic of the University Hospital, an opportunity was presented of studying a local type of reaction following injection of insulin.

Case II.—The patient, a young girl, aged sixteen years, had a history of diabetes of one year's duration. Insulin administration was begun August 29, 1927, beginning with 5 units of U20 Lilly and increasing to 10 units on September 9 and to 15 units on October 10. The same preparation was used in each instance, and at no time did any local reaction occur. On October 15, she began the use of Stearn's insulin U40, injecting 15 units each time into the arms and legs. After each of these injections the patient had a local reaction, occurring immediately following the injection and consisting of local blanching, swelling and considerable surrounding erythema, which was soon followed by an induration the size of a large walnut, tender to touch but causing no local pain. These indurated areas persisted for more than four weeks before any diminution in size was noted. Each subsequent injection with the same preparation was followed by a similar local

reaction irrespective of the site used. Similar injections of the same lot of Stearn's insulin given to other diabetic patients during the same period caused in no instance a similar reaction. Because of the occurrence of these local reactions, on October 27, 1927, the patient discontinued the use of the Stearn's preparation and began the use of U40 Lilly. No local reactions have since been noted. Skin tests on this patient showed the following results: marked reaction with the original lot of Stearn's insulin; slight to moderate reaction with U40 Lilly (2 different lots); slight reaction with U20 Mulford and with the insulin diluting fluid; negative reaction with purified insulin of Abel and with pork extract and a slight to moderate reaction with beef extract, this reaction being of no greater intensity than that obtained on many normal individuals with the same extract (Fig. 5).

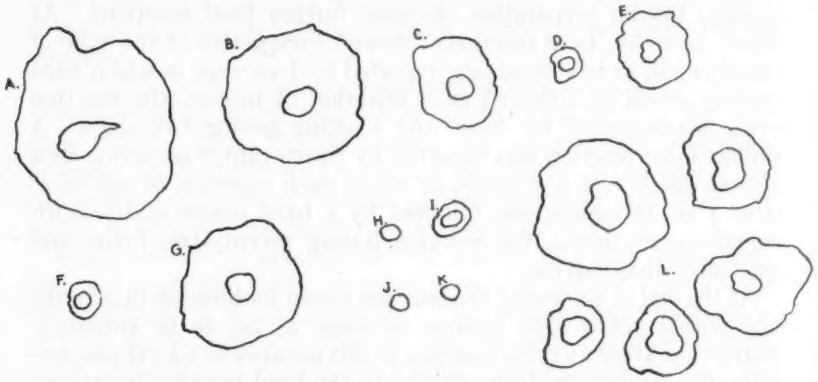

FIG. 5.—Studies on patient L. S. *A*, skin test with insulin—Stearns U40; *B*, skin test with insulin—Lilly U40; *C*, skin test with insulin—Mulford U20; *D*, skin test with insulin—Abel; *E*, skin test with insulin diluting fluid; *F*, skin test with pork extract; *G*, skin test with beef extract; *H*, insulin—Lilly U40; into sensitized site; *I*, insulin—Lilly U40 into nonsensitized site (control); *J*, insulin—Abel into sensitized site; *K*, insulin—Abel into nonsensitized site (control); *L*, insulin—Stearns U40 into normal persons (control cases).

The negative reaction to the purified insulin of Abel would seem to exclude any true sensitivity to insulin protein itself as the cause of the reaction and make it seem likely that the reaction was due to some irritating quality contained in the particular lot of insulin used and obtained in the extracting process. This possibility is further strengthened by the fact that skin tests with the same Stearn's insulin preparation on 10 other diabetic patients showed in every instance slight to moderate reactions.

The serum of the patient with the local reaction was also studied for the presence of reagins by the method herein described with entirely negative results.

Comment. In reviewing the results of these observations several important facts stand out prominently. In the first place, it has been demonstrated that in our first patient as a result of repeated injections of insulin, there had been acquired a specific form of

hypersensitiveness to insulin protein manifesting itself as a generalized urticarial eruption with edema and dependent, not as has been previously thought, on a sensitivity to the extraneous protein of the pancreas obtained in the extracting process but rather to a specific hypersensitiveness to insulin protein itself, irrespective of its biologic source. This form of hypersensitiveness is apparently not accompanied by the presence of anaphylactic or complement-fixing antibodies in the serum of the patient, but after the occurrence of the reaction, both precipitins and specific reacting substances or reagins to insulin were demonstrated on several occasions in the patient's serum, the precipitins disappearing soon after the reaction, the reagins persisting for more than ten weeks, and in the skin a high degree of cutaneous sensitivity to insulin was present and is still demonstrable. On the other hand, in the second patient the injection of one particular lot of insulin was followed by a local reaction, manifesting itself by indurated nodules lasting four to six weeks before disappearing, obviated by change in the preparation of insulin used and apparently dependent, not on a specific hypersensitiveness to insulin protein itself, but rather upon some irritant quality of the particular preparation producing the reaction. From these observations it is doubtful whether this type of reaction can with justice be included immunologically in the class of local hypersensitiveness or local anaphylaxis or as a form of Arthus phenomenon occurring in the human being, since it differs from the latter conditions in that they are as a rule dependent on a previously existing sensitivity acquired usually by previous injection and that subsequent injection of the same antigen irrespective of its preparation produces the same reaction. It seems more logical, therefore, to regard this type of reaction as chemical rather than biologic in character.

The demonstration of reagins in the patient reported is not only unique in relation to insulin hypersensitiveness but is of considerable immunologic importance. As has been previously stated, until recently the presence of reagins had only been demonstrated in patients with hay fever or bronchial asthma and it has, therefore, been thought by Coca[21] that this type of antibody is apparently specific for those conditions subject to hereditary influence, in other words, that it was the atopic antibody. The demonstration of reagins in the serum of worm-sensitive individuals by Rackemann,[22] and more recently by Brunner,[23] has caused a modification in this viewpoint so that Coca[21] now believes that this antibody may be present in nonatopic individuals and that it is not strictly the atopic antibody. This conviction is further strengthened by the present study since it has been shown, apparently for the first time, that reagins and cutaneous sensitivity to a specific antigen has been found in a condition accompained by urticaria occurring in a nonatopic individual as part of an acquired or induced form of hypersensitiveness. Although insulin is not a typical atopen, never-

theless, its reagin production is accompanied by constitutional manifestations in the form of urticaria and edema which apparently distinguishes the insulin antibody from the type of antibody present in worm-infested individuals.

The disappearance of the antibodies from the serum, four months after the occurrence of the reaction, is rather interesting, particularly since at this time a high degree of cutaneous sensitivity was still demonstrable. In this and in other respects insulin hypersensitiveness closely resembles serum disease: both are acquired or induced forms of hypersensitiveness; in both conditions the reaction does not occur following the initial or sensitizing injection but rather after a variable latent period; urticaria is present in both as part of the reaction and in both instances, following the reaction positive skin tests to the offending antigen are obtained and antibodies are detectable in the patient's serum, precipitins and anaphylactins in the case of serum disease and precipitins and reagins in insulin hypersensitiveness. These antibodies persist in both conditions only for a short period after the occurrence of the reaction, the precipitins disappearing first, the other antibodies at a later time whereas cutaneous sensitivity persists apparently for considerable period of time.

These similarities between serum disease and insulin hypersensitiveness are rather striking and make it seem justifiable to include the latter together with serum disease and drug hypersensitiveness in the group of acquired or induced hypersensitiveness in contradistinction to the natural or hereditary form comprising at present hay fever and asthma. The close similarity between the reaction in serum disease and drug hypersensitiveness has been particularly stressed by Coca,[24] and they differ apparently merely in the type of antigen causing the reaction. This is also true of the antigen in insulin hypersensitiveness, but in the latter condition we have in addition a difference in one of the types of antibodies produced.

The above studies also provide an additional example of immunologic specificity, since it has been shown that distinct hypersensitiveness to insulin protein irrespective of its biologic source, was present whereas no sensitivity to the proteins of other tissues of the same animal could be demonstrated. In this respect, insulin protein is similar to lens protein, which is immunologically similar to the lens protein of other species but different from the proteins of other tissues of the same animal. These facts are in accordance with the statement by Wells,[25] that substances of the animal body concerned in its metabolic function such as lens protein, insulin, trypsin, and so forth, should be similar for all species whereas the proteins of other tissues may be different.

Finally, it may be well to mention a few words as to treatment. Fortunately in the above patient further insulin treatment has not been necessary, but should the occasion arise, from the experience

in other reported cases, and the fact that after the occurrence of the reaction, injection of 10 units caused no reaction whereas 15 units did, small doses at intervals may prevent a reaction. If this fails, desensitization may be attempted. It will be of great interest to observe and to report in the further course of this patient whether in the absence of reagins in the serum insulin injection will now produce a similar reaction, and also if such a reaction does occur, whether the appearance of reagins precedes or follows it, thus attempting to indicate whether these antibodies are the result of the reaction rather than the cause of it.

Summary. As a result of the injection of insulin, a fortunately small percentage of individuals may display a reaction of hypersensitiveness to the insulin protein in its purest form, as exemplified in the first patient herein reported. This type of reaction occurred after a number of injections had been given, manifesting itself by generalized urticaria and edema; showing by skin test a high degree of cutaneous sensitivity to insulin, irrespective of its biologic source. By the method of local passive transfer of Praussnitz and Kustner on several occasions, reagins to insulin protein could be demonstrated in the patient's serum, these antibodies disappearing four months after the occurrence of the reaction. Except for precipitins, which were present only for a short time after the reaction, other types of antibodies were not demonstrable. The striking similarity between the manifestations of hypersensitiveness to insulin, serum disease and drug hypersensitiveness is stressed and it is believed that these three forms of hypersensitiveness should be properly placed in the group of acquired or induced hypersensitiveness, differing but slightly in their clinical manifestations and chiefly in the character of the antigen inducing the reaction and in one of the types of antibodies induced. In the treatment of this type of case, reduction in the dosage given at one time should be tried, and if this fails desensitization should be attempted. A second type or local form of reaction after insulin injection occurs usually following change in site of injection or in the preparation of insulin used, as in the second case herein reported and is characterized by the formation of indurated nodules persisting four to six weeks before disappearing spontaneously. This type of action has been shown to be dependent not on a specific local hypersensitiveness to insulin protein similar in character to the local anaphylaxis of the Arthus phenomenon but rather to an irritant quality of the particular lot of insulin producing the reaction and probably dependent on some physical or chemical rather than biologic characteristic of this preparation.

Finally, additional evidence indicative of immunologic specificity is presented, in that as with lens protein, insulin protein derived from various species of animals is immunologically and probably chemically similar to the insulin protein of all other species of animals but different from the proteins of other tissues of the same animal.

NOTE.—In conclusion the writer wishes to take this opportunity of expressing his appreciation to Miss Elizabeth Yagle for her assistance in carrying out the complement-fixation tests, to Dr. J. A. Kolmer, for his many valuable suggestions, to Dr. Russell Richardson for permission to utilize some of the clinical material for study and to Dr. J. J. Abel for the purified insulin used in this study.

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BENIGN NEOPLASMS OF THE BRONCHUS.

REPORT OF A CASE OF FIBROLIPOMA OF THE LEFT MAIN BRONCHUS REMOVED THROUGH THE BRONCHOSCOPE.

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WITHIN the past few years, the number of neoplasms which have been observed and completely removed by means of the bronchoscope has appreciably increased. With the more general recourse to bronchoscopy in obscure chest conditions, this is to be expected. Benign neoplasms are benign only in the histologic sense. As they

grow, they cause obstruction of the air passage and interfere with the respiratory function and the vital capacity of the individual. In addition, they favor the production of bronchiectasis in the structures which are distally located. So that the recognition and removal of one of these neoplasms constitutes a life-saving measure.

Up to the present time, there are records of ten neoplasms that have been removed bronchoscopically. It appears that von Eicken[1] was the first to diagnose and remove a benign neoplasm of the bronchus by means of the bronchoscope. In 1907, he reported the complete removal of an enchondroma from the left main bronchus of a man aged forty-one years. Three years later Speiss[2] reported the removal of a fibrous polypoid tumor from the right main bronchus of a man aged forty-seven years. This was done by means of bronchoscopy through a tracheotomy opening. Jackson[3] mentions the removal of a fibroma from the lip of the left upper lobe bronchus in a boy aged sixteen years, in his textbook. The same author removed an obstructing tumor from the right main bronchus of a man aged thirty-five years. This was pedunculated and proved after removal to be an endothelioma.[4]

Another fibroma was removed from the left main bronchus by W. Pfeiffer.[5]

Wessler and Jaches[6] mention the removal of a fibroma from the left main bronchus of a man aged twenty-eight years. This was done by Yankauer in 1920. They speak of the effects of obstruction caused by the tumor, and the remarkable recovery which the patient made after its removal.

Orton had a similar experience to that of Jackson. He[7] removed a a neoplasm from the right main bronchus of a man aged twenty-nine years. Jesberg reported[8] the removal of a polyp from the left main bronchus in a six-year-old boy. Two more cases of fibroma of the bronchus were recorded in the past year. Zinn[9] removed a fibroma from the left main bronchus of a man aged fifty-two years. The second case was reported by Burrell and Trail who had[10] under their care a lady aged twenty-three years. She had had hemoptyses for over a year. Physical examination and Roentgen study revealed an obstruction in the left lower lobe bronchus. Negus bronchoscoped this patient and removed piecemeal, by means of cup-shaped forceps, a tumor mass which proved to be a fibroma.

To the above I wish to add the report of my experience in a case which finally yielded a large fibrolipoma of the left main bronchus.

Case Report. A man, aged forty-seven years, was first seen at the Jewish Hospital of Brooklyn, September, 1927. His trouble dated from February, 1926, when he began having pain in his left upper chest, attacks of dyspnea, cough and later some expectoration. These attacks of dyspnea gradually became worse and more frequent. During the period of his illness he had been hospitalized three times. Each time a thorough study of his condition was made, yet at no time was bronchoscopy considered.

In addition he had been sent to several places far from home. Not only was he unimproved, but upon his return from the last place he was considerably underweight and very sick.

His attacks of dyspnea were inspiratory. During the attack his mouth was wide open, the infraclavicular and supraclavicular spaces were markedly retracted, the face was anxious and relief came with expiration. In the beginning these attacks lasted a few minutes and came three or four times a day. At the end of a year of illness the attacks were practically continuous. As a result of the hospital studies it was thought that he was suffering with a myocardial insufficiency, which was the basis for his asthma. He had what was thought to be a diffuse bronchopulmonary fibrosis and a pulmonary emphysema which were thought to be the factors in the production of his myocarditis. Tuberculosis, although suspected, could not be proven. The sensitization tests revealed that he was sensitive to dust. As a result, he was given a series of injections of dust suspension which, however, d d not help his condition. Adrenalin and ephedrin were of value in relieving his attacks in the beginning, but their efficacy soon was lost. Codein afforded him the greatest relief over a long period of time. He was also considered and treated as a neurotic.

At the time he was first referred for bronchoscopy the patient had been expectorating blood for several weeks. At bronchoscopy the left lower lobe bronchus and all its visible branches were found to be dilated. Pus was seen to be coming from the terminal branches with each expiration. An attempt was made to investigate the upper lobe region at this time, but this was abandoned because of the difficulty of handling the patient and because of his lack of coöperation. At this time mapping with lipiodol revealed many bronchiectatic cavities behind the heart (Fig. 1).

The patient was not seen again until three months later. At this time the physical signs indicated a stenosis of the left bronchus with atelectasis of the lung on that side and a displacement of the trachea and heart to the left. Bronchoscopy was performed with a 9-mm. Jackson tube. A large mass was encountered which filled the lumen of the left main bronchus just before the upper lobe branch is given off (Fig. 2). During inspiration the tumor mass disappeared and during expiration the mass returned to view. The left main bronchus was markedly dilated where the neoplasm came into contact with it. This condition did not exist at the previous bronchoscopy three months before. The attachment of the neoplasm could not be made out. It was described as a firm, large and irregularly round mass, covered with mucous membrane and moving freely with inspiration and expiration. It was thought to be a pedunculated tumor whose origin was in the upper lobe bronchus. An attempt was made to detach the mass with grasping forceps, but it appeared to be too firmly attached to be delivered in this way without danger to the patient. Arrangements were made for a future bronchoscopy when adequate preparation for the removal of the growth would have been made. In the meantime fluoroscopic and Roentgen study with the aid of lipiodol was carried out. The right bronchial tree was apparently normal, while the left side of the chest was entirely obstructed (Fig. 3).

The oblique view of the chest, however, revealed the cause of the obstruction. A bilobed tumor was outlined by the lipiodol (Fig. 4). On December 21 a third bronchoscopy was performed. Bronchoscopy confirmed the presence of a bilobed tumor. The posterior lobe was cystic and fully one and a half times the size of the anterior firmer mass. The cystic mass appeared to spring from the posterior surface of the smaller anterior one. The cyst entirely filled the lumen of the bronchus during both phases of respiration. A pair of rotation forceps were used to rupture the cyst. This was readily accomplished by merely grasping the cyst, and a quantity

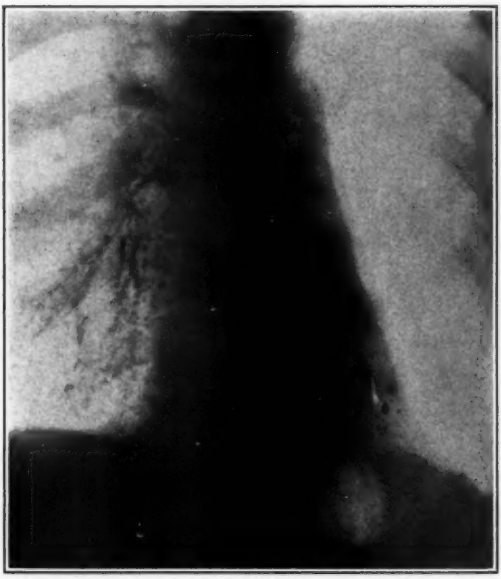


FIG. 1.—Showing condition of chest when first seen. There are numerous bronchiectatic cavities behind the heart.

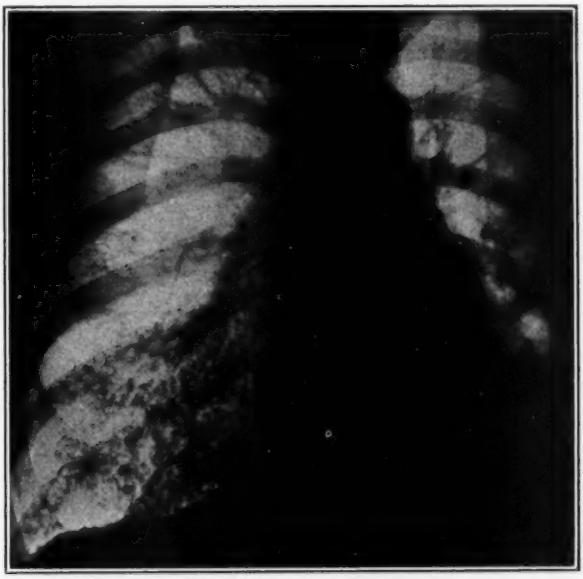
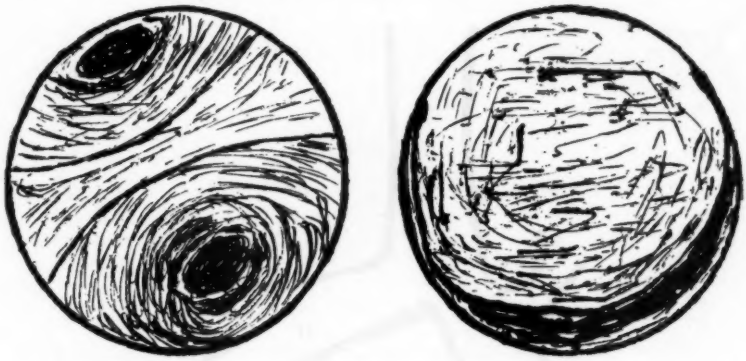


FIG. 3.—Three months after Fig. 1. Anterior view, showing a complete obstruction of the left main bronchus with collapse of the lung and displacement of the heart and trachea to the left. The right side of the chest is somewhat emphysematous and the bronchial tree is outlined by the lipiodol.

FIG. 4.—Anteroposterior view of chest after rupture of cyst, showing patency of upper lobe bronchus.

FIG. 7.—Low power. Fibrolipoma of bronchus.

of thin fluid escaped into the bronchus. With the rupture of the cyst, the left lung became aërated and the trachea and heart were replaced to their relative normal positions. The attachment of the neoplasm could now be made out. The mass was of sessile attachment and sprang from the roof of the main bronchus just before the upper lobe branch. The view of the upper lobe branch was still obstructed by the remaining firm tumor. At this time the attachment was partly severed, and it was felt that removal of the tumor could be accomplished at the next bronchoscopy. The passage of a wire snare around the tumor was attempted many times, but was unsuccessful. Careful study was made of the excursion of the neoplasm. It was estimated that the tumor mass moved as much as $1\frac{1}{4}$ inches during each phase of respiration.



A *B*

FIG. 2.—*A*, normal image looking down the left main bronchus just before the upper lobe branch is given off; *B*, neoplasm filling entire lumen of bronchus instead of image as shown in *A*.

The rupture of the cyst had an immediate beneficial effect upon the patient. He could now breathe freely and did not tire readily as before. The introduction of lipiodol into his left lung demonstrated that, despite the presence of the firm tumor, he now had complete patency of all the bronchi (Figs. 5 and 6).

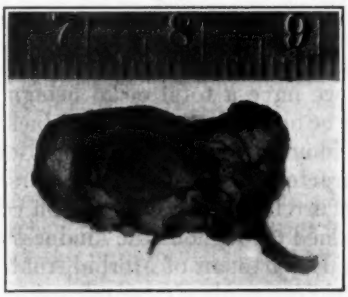


FIG. 5.—Neoplasm, fibrolipoma of main bronchus, removed from left.

Three weeks later bronchoscopy was again performed. Complete removal and extraction of the tumor was accomplished at this time. The

attachment of the tumor was attacked with a Yankauer forceps and gradually severed. Upon removal the mass measured 23 by 16 by 6 mm. (Fig. 7). Springing from the upper part of the posterior wall there was seen a tab of loose tissue which represented the remains of the cyst which had ruptured. Dr. Hala reported that the tumor was a fibrolipoma (Fig. 7, photomicrograph). There was no active bleeding following the removal of the neoplasm. The expectoration was slightly blood tinged for a few hours. Within six weeks following the removal of the growth the patient had gained 30 pounds and was back at his work for the first time in two years. Bronchoscopy three months after removal of the tumor revealed that the dilatation caused by the neoplasm had almost entirely disappeared. The bronchiectasis of the left lower lobe was markedly improved.

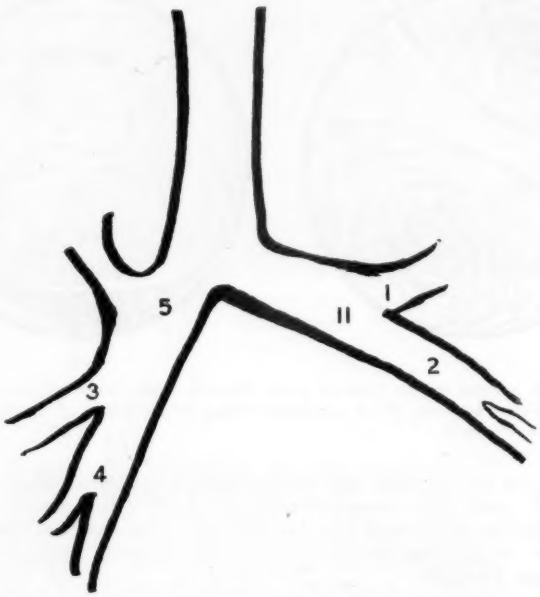


FIG. 6.—Bronchial tree, showing distribution of neoplasms.

If we add to the bronchoscopic cases, 15 cases which have been found at autopsy, we have a total of 26 benign neoplasms of the bronchus. It must be noted that the cases of Jackson (endothelioma and of Orton (carcinoma), were not suspected of being malignant and had gross characteristics of benign tumors. In neither case has there been a recurrence. My information concerning these 15 cases has been obtained throughout the kindness of Drs. Klemperer and Reissner of the Department of Morbid Anatomy of the Mount Sinai Hospital. Reissner made a comprehensive study of the literature and added a case of adenoma observed at autopsy.[11]

These new growths usually cause a secondary bronchiectasis in the structures which are located toward the periphery. Biermer, in 1860,[12] called attention to the influence which bronchial tumors

have upon the production of bronchiectasis in the structures beyond the growth. He showed that there was increased intrabronchial pressure during expiration in these cases. The ball-valve action of the tumors seemed to influence expiration first. This is, of course, aggravated by the cough which is usually present in tumor cases and which is increased by the bronchiectasis. In addition these factors influence the elasticity of the bronchial walls so that there is a gradual thinning and weakness of them.

TABLE I.—NEOPLASMS OF THE BRONCHUS.

Neoplasms bronchoscopically removed.	Removed bronchos.	Observed at autopsy.
Adenoma*	..	4
Carcinoma†	1	
Chondroma	1	2
Endothelioma†	1	
Fibroma	5	1
Fibrolipoma	1	
Lipoma	..	2
Lipochondroadenoma	..	1
Polyp or polypoid tumor	2	4
Aberrant thyroid	..	1
Total	11	15
Grand total		26

* Three polyps and one adenoma showed malignant changes.
† Unsuspected at time of removal.

TABLE II.—DISTRIBUTION OF NEOPLASMS ACCORDING TO BRONCHI.

Right main.	Right middle.	Right lower.	Left upper.	Left main.	Left lower.
Carcinoma 1	Adenoma 1	Adenoma 2	Fibroma 1	Adenoma 1	Fibroma 1
Chondroma 1	Lipoma 1	Fibroma 1		Chondroma 1	Lipoma 1
Endothelioma 1	Polyp 1	Lipochondro-adenoma 1		Fibroma 3	
Polyp 2				Fibrolipoma 1	
Thyroid, aberrant 1				Polyp 4	

As a result of the above experience and that of others, it is evident that neoplasms of the bronchus can be removed by means of peroral bronchoscopy under local anesthesia. Even though the neoplasm is of sessile attachment and fairly large, bronchoscopic removal appears to be feasible.

It is demonstrated once again that obscure chest conditions should always include in their routine study, a bronchoscopic examination. It is essential that the importance of the application of bronchoscopy in these cases shall not be overlooked. For in this class of case, bronchoscopy can save the individual from a life of invalidism and early death. With the more general use of bronchoscopy it is expected that the finding of benign neoplasms of the bronchi will not be so uncommon in the future.

Summary and Conclusions. 1. An analysis of the literature reveals a fairly large variety of benign, pulmonary neoplasms. The number of neoplasms which will be removed in the future is expected to show an increase, for the increasing recognition of the value of bronchoscopy and its more frequent application justify this prediction.

2. A case is cited in which a patient with pulmonary symptoms was treated for tuberculosis, asthma, chronic pulmonary fibrosis and myocarditis, while the basis for his trouble was the presence of a fibrolipoma in his left main bronchus. This case demonstrates the importance of including bronchoscopy in the study of pulmonary conditions with obscure or atypical symptoms. It also demonstrates that we can hope to save the lives of patients who have benign neoplasms of the bronchus by a timely bronchoscopy.

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REVIEWS.

CONSTITUTIONAL INADEQUACIES: AN INTRODUCTION TO THE STUDY OF ABNORMAL CONSTITUTIONS. By NICOLA PENDE, M.D., Professor of Clinical Medicine, Royal University of Genoa, Italy. Translated by SANTE NACCARATI, M.D., SC.D., PH.D. Pp. 270; 11 illustrations with tables. Philadelphia: Lea & Febiger, 1928. Price, $3.50.

THIS translation reveals the author, easily, as a foremost leader in the constitutional school and it is hoped the subject shall gain in popularity in America where interest in the movement has thus far been scant.

In range the chapters include the entire body, with additional ones giving helpful suggestions in therapy together with the author's analysis of his intensive study of the individual human biotype.

By the diatheses are meant: "certain anomalous or morbid temperaments which no longer belong within the confines of normal variability of temperaments but already begin to represent potential disease conditions." The principal ones are: (1) Arthritic (exudative and hypersecretory); (2) neuro-endocrinopathic; (3) psychopathic; (4) heredo-syphilitic; (5) heredo-tuberculous; (6) heredo-neoplastic.

Happily, a glossary defines the many new terms.

N. Y.

SURGICAL ANATOMY. By GRANT MASSIE, M.B., M.S. (LOND.), F.R.C.S. (ENG.). Pp. 413; 121 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $5.50.

THERE is a gradually increasing tendency in medical schools to correlate more thoroughly the various academic subjects with the clinical aspect of disease. Anatomy, physiology and chemistry studied from the standpoint of their clinical significance will be infinitely more easily remembered by the student, as well as being more helpful to him later as a clinical man.

The author has endeavored to accomplish this as far as anatomy, physiology and surgery are concerned in this work on Surgical Anatomy. The reader must, however, bear in mind that no work

of this size and character can be used in any sense as a full treatise on either of the correlated subjects. Bearing these limitations in mind, however, the student will find this little book a very pleasing, interesting and helpful adjunct to an otherwise tiresome and dry phase or period of his student days.

E. E.

ANIMAL BIOLOGY. By J. B. S. HALDANE, and JULIAN HUXLEY. Pp. 344; 122 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $2.50.

WE often hear that the English boy progresses more rapidly in his education than does his American cousin. The editors state in their introduction that this book is intended to give the necessary biological background to the average boy of less than sixteen years of age. If it is well fitted for this purpose, we feel inclined for the first time to agree with the opinion expressed in the opening sentence. Development and heredity, exchange of matter and energy, the nervous system and the internal environment and evolution receive the masterly concise treatment that one would expect from a Haldane and a Huxley. But whether, even with a glossary that extends from "allelomorph" to "zygote," the average sixteen-year-old boy will or can digest such material is a matter of considerable doubt. In any case, for the medical man who wishes to review or extend his biologic knowledge, there will be much of interest and instruction in this latest child of the Clarendon Science Series.

E. K.

DIAGNOSIS AND TREATMENT OF DISEASES OF THE STOMACH: WITH AN INTRODUCTION TO PRACTICAL GASTROENTEROLOGY. By MARTIN E. REHFUSS, M.D., Assistant Professor of Medicine, Jefferson Medical College. Pp. 1236; 519 illustrations. Philadelphia and London: W. B. Saunders Company, 1927. Price, $12.00.

INTO this volume is assembled a vast amount of information relating to the diagnosis and treatment of gastric and allied diseases. Although chapters and subsections by Chevalier Jackson, Willis F. Manges, John H. Kolmer, J. Alexander Clarke, Louis F. Clerf and John B. Deaver are included, 93 per cent of the text is from the author's own pen. Diagnostic procedures are dealt with in great detail even to the extent of considering the selection of a special kind of room for a laboratory, its lighting and ventilation and the arrangement of the tables and apparatus (illustrated); also, in connection with Roentgen ray study, of discussing the kind

of tube to be used and giving the roentgenologic technique. The author's own work on gastric analysis and that of his associates is presented most completely, much of it appearing almost as in the original journal articles. The illustrations are excellent and especially the schematic outlines, of which the author is a master. References to the literature are copious and other writers are quoted freely, sometimes to the extent of pages; this has an advantage over the more common method of rewriting their material in less satisfactory language.

The chief criticism of the book involves its unnecessary size. This is due to a failure to deal completely and finally with a subject in its proper place. In consequence there result not only many repetitions in paragraph after paragraph and chapter after chapter, but also for the reader much confusion of thought and much waste of time. For instance, on page 660 under the heading "Symptoms of Duodenal Ulcer" the characteristic type of pain is discussed, then on the next page under "Physical Examination" are taken up serially the importance of symptomatology, the duration of symptoms, the nature and food relationship of the pain (already discussed), certain conditions that influence a recurrence of symptoms, as infection and the seasons, food relationship of the pain again and, finally, in the last few sentences, the physical signs. A revision of the work to eliminate these conditions would reduce the size of the book by several hundred pages and greatly enhance its value, while lowering its price. T. M.

LECTURES ON THE BIOLOGIC ASPECTS OF COLLOID AND PHYSIOLOGIC CHEMISTRY. A series of lectures given at the Mayo Foundation and the Universities of Wisconsin, Minnesota, Iowa, Washington (St. Louis) and the Des Moines Academy of Medicine, Iowa, 1925–1926. Pp. 244; illustrated. Philadelphia: W. B. Saunders Company, 1927. Price, $2.50.

THE lectures cover a number of important aspects of recent investigation in the field of colloid chemistry from a biologic standpoint. Professor Milliken has a chapter on the principles underlying colloid chemistry. Professor M. H. Fischer deals with colloid chemistry in biology and medicine. Professor Chambers discusses the physical properties of protoplasm, and Professor Gortner, adsorption and vital phenomena. Professor Burton's lecture is on the physics of the ultramicroscope and optical properties of colloid particles. The concluding chapter is by Professor Bovie on the biologic effects of light. At the present time these important aspects of colloid chemistry are matters of interest—not only to chemists, but also to physicians and biologists. The book will be very welcome to the many who were not able to attend the lectures. B. L.

PERCIVAL'S MEDICAL ETHICS. Edited by CHAUNCEY D. LEAKE, Associate Professor Pharmacology, University of Wisconsin. Pp. 291; 10 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, $3.00.

NOT only is the complete text of Percival's *Medical Ethics* given in this book (with a facsimile of the title page), but it is preceded by a valuable introductory essay and succeeded by five appendices of the other systems of importance in the development of medical ethics. The modest rôle of "editor" assumed by Mr. Leake is, therefore, a considerable understatement. The book is both a well-indexed source book for Percival, the Hippocratic oaths and the pronouncements of the American Medical Association and also a valuable commentary on Percival, his works and their influence.

E. K.

HANDBOOK ON DIET. By EUGENE E. MARCOVICI, M.D. Pp. 323. Philadelphia: F. A. Davis Company, 1928. Price, $3.50.

I AGREE with the author of the book that there has long been a need for just such a book to fill the gap between the medical profession and the average layman, who knows nothing of such matters. This book ably fills that gap. In many places in the book we feel the foreign influence in the number of meals served. However, this is always covered to meet the three meal day, which is so necessary in most of our institutions. Nowhere do I know of a better chapter on the contamination of foods. The chapter on "Diet in Disease" would be improved if some menus were suggested for use in typhoid and other febrile cases. The section on "Diseases of the Intestinal Tract" is especially to be commended for giving not only the treatment itself but also its why and wherefore. One cannot read this chapter without feeling better prepared. The chapter on Special Diets and Food Fads is splendid. The book should be bigger. I would like to see a special chapter on preoperative and postoperative feeding. More space should be allotted to diet for pernicious anemia.

E. M.

SCHIZOPHRENIA (DEMENTIA PRÆCOX). A Series of Research Publications. Volume V. Pp. 491; 61 illustrations. New York: Paul B. Hoeber, Inc. Price, $7.50.

THIS series of papers read before the Association of Research in Nervous and Mental Diseases, is happily attended by the discussions. Such a rendering of the difficult subject of Schizophrenia, by an orchestra of thirty-one collaborators, is stimulating. Of the

many problems in this disorder, only a few have been solved, but the enthusiasm of the workers and the new avenues of approach, must eventually yield results.

The term dementia præcox is becoming obsolete. Among other reasons, some subjects do not progress to dementia, and the age when the disease first appears may be far beyond that previously held for præcox. The disease is without definite pathology. Endocrine dysfunction does not appear to be a cause. The one almost constant finding is an abnormally low basal metabolism in about one-half the subjects and a low tendency in those remaining. Under treatment is a touching reference to the work at the Gheel Colony. If there be any measure other than kindness, so helpful to those mentally ill, the reviewer is not aware of it.

N. Y.

SPECIAL CYTOLOGY. (THE FORM AND FUNCTIONS OF THE CELL IN HEALTH AND DISEASE) A TEXTBOOK FOR STUDENTS OF BIOLOGY AND MEDICINE. EDITED BY EDMUND V. COWDRY, The Rockefeller Institute for Medical Research. Two volumes. Pp. 1376; 693 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $20.00.

THIS important work may be regarded as supplementary to "General Cytology" published by the University of Chicago Press in 1924, in which were discussed the fundamental principles of structure and function which cells possess in common. The purpose of the "Special Cytology" is to present a detailed account of the principal types of cells that make up the body, and particularly the human body. Thirty-five distinguished investigators in different fields of biology and medicine have contributed chapters on the particular subjects of their research, and thus each subject is dealt with in a much more authoritative manner than could possibly be done by a single author. The general plan of the book is stated in the introduction: "The purpose of cytology is not only to gain an accurate morphological knowledge of the cell, but also to learn its chemical constitution, the nature of its organs, the function of its nucleus and cytoplasmic structures, etc. The condition of the cell, however, is closely related to that of its medium. Cytology, therefore, must deal not only with the anatomical and chemical constituents of the tissues, but also with the humors which control this metabolism."

It is of course obvious that, even with the subdivision of labor that obtains in this book, each topic will be considered mainly from the point of view with which the particular author has been identified. It is equally obvious, however, that conscientious efforts have

been made to include the other points of view, in some cases with conspicuous success.

The scope of the book may be seen from the table of contents: Introduction by Alexis Carrel; The Skin and Its Derivatives, by E. V. Cowdry; The Mucous Membrane of the Nasal Cavity and the Paranasal Sinuses, by J. Parsons Schaeffer; The Epithelium of the Lower Respiratory Tract, by William Snow Miller; The Salivary Glands, by D. L. Stormont; The Gastric Glands, by R. R. Bensley; The Intestinal Epithelium, by Charles Clifford Macklin and Madge Thurlow Macklin; The Cytology of the Liver and Its Functional Significance, by Frank C. Mann; Cytology of the Pancreas, by Eugene L. Opie; The Erythrocyte, by E. B. Krumbhaar; The Lymphocytes and Plasma Cells, by Alexander A. Maximow; The Myeloblast, by Hal Downey; The Granular Leukocytes, by C. H. Bunting; The Macrophages or Histiocytes, by Alexander A. Maximow; The Structure of the Hypophysis Cerebri of Man and of the Common Laboratory Mammals, by Percival Bailey; The Pineal Gland, by Frederick Tilney; The Thyroid, Parathyroids and Thymus by David Marine; The Suprarenal Bodies, by G. N. Stewart; Renal Tubules, by G. Carl Huber; Cartilage and Bone, by P. G. Shipley; The Synovial Membrane of Joints and Bursæ, by J. Albert Key; Striated and Smooth Muscle, by Edward B. Meigs; Cardiac Muscle by A. E. Cohn; The Specialized Systems of the Heart, by T. Wingate Todd; Visual Cells and Retinal Pigment, by Leslie Brainerd Arey; Cytology of the Internal Ear, by George E. Shambaugh; The Internal Architecture of Nerve Cells, by E. V. Cowdry; The General Relation of Histological Character to Function in Mammalian Neurons, by E. F. Malone; The Sympathetic Nerve Cells, by Albert Kuntz; Neuralgia and Microglia, The Interstitial Tissue of the Central Nervous System, by Wilder Penfield; The Cytology of the Cerebrospinal Pathway, by G. B. Wislocki; Cytology of the Ovum, Ovary and Fallopian Tube, by G. W. Corner; Cellular Changes in the Fluid of the Mammalian Vagina, by Charles R. Stockard; The Cytology of the Mammary Gland, by Leo Loeb; Interstitial Cells of the Testis, by A. T. Rasmussen; The Male Germ Cells, by Charles W. Metz; The Seminal Vesicles, Prostate and Bulbo-urethral Glands, by Charles Clifford Macklin.

Each section is preceded by a separate table of contents, of which the section on the skin (selected at random) may serve as an example. Section II. Skin and its Derivatives. General Considerations: Mechanical protection; Chemical and physical properties of surface layer; Protection against fluids and gases; Protection against light; Protection against extremes of heat and cold; Selective nervous sensibility; Effect of substance of epidermal origin on internal tissues; Influence of internal organs on skin; Allergic reaction. Epidermis: Shape of cells; Physical consistency of cells and nuclei; Nuclei; Mitochondria; Golgi apparatus; Intracellular fibrils; Inter-

cellular bridges; Melanin; Keratohyalin; Keratin; Fatty substances; Nerve and vascular supply; Specific inclusions occurring in diseases due to filterable viruses; Other substances which have been reported. Cutaneous Glands; Hair and Nails. Bibliography.

The printing and paper of the book are excellent; the many illustrations deserve particular praise. It is to be expected that this book will be welcomed by all who have read "General Cytology." Indeed "Special Cytology," since it deals particularly with the cells of the mammalian and especially the human body, will be most useful and helpful to students of medicine in its various fields. It can be warmly recommended as a reference worked along with important phases of physiology, pathology and anatomy.

B. L.

THE MECHANICS OF THE DIGESTIVE TRACT. By WALTER C. ALVAREZ, M.D., Associate Professor of Medicine, University of Minnesota (The Mayo Foundation). Second edition. Pp. 447; 100 illustrations. New York: Paul B. Hoeber, Inc., 1928. Price, $7.50.

IN the first edition of this book five years ago Alvarez gave the first complete statement of his gradient theory for gastrointestinal motility. Since that time much support for it has been gained in his own research and clinical work and in that of others. A more mature and conservative point of view is detected in this edition and a more obvious effort to separate facts from theory. The general scope of the work is widened so as to make available much important information regarding the digestive tract that has grown out of clinical and laboratory research. With Cannon's and Carlson's books it ranks as an important American contribution to the literature on the mechanics of digestion.

T. M.

ANTHELMINTICS AND THEIR USES IN MEDICAL AND VETERINARY PRACTICE. By P. N. CHOPRA, Professor of Pharmacology, Calcutta School of Tropical Medicine and Hygiene and ASA C. CHANDLER, Professor of Biology, Rice Institute, Houston, Texas. Pp. 291; 5 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $5.00.

A CAREFUL perusal of the book shows that the subject has been carefully covered including as it does a general consideration on anthelmintics giving detail of the chemical composition of these preparations, their physiological action and their effect on parasites. Likewise the dosage and mode of administration is indicated.

The authors made a rather useful separation as to the use of anthelmintics for the parasites of the intestines, as applied to Cestodes, such as male fern and allied drugs and those recommended for Nematodes with special reference to carbon tetrachloride and carbon derivations and the essential oil groups, such as oil of chenopodium, santonin, etc.

The authors in mentioning the recent method of Rivas in the removal of intestinal parasites by the application of salt solution at 45° to 47° C., unfortunately by an oversight give the amount of liquid as 2 gallons, instead of no more than 2 liters as recommended in the original publication.

D. R.

THE ULTRAVIOLET RAYS. By ARNOLD LORAND, M.D. Pp. 258. Philadelphia: F. A. Davis Company, 1928. Price, $2.50.

BEGINNING with a general discussion of the action of ultraviolet rays, the author proceeds to describe the treatment of various pathological conditions by the means of those rays. A large part is devoted to their use in preventing loss of color and falling of the hair. The importance of the internal action of the ultraviolet rays is emphasized. Other therapeutic measures aiding the ultraviolet treatment are given and discussed.

This interesting book is written in a rather popular style and with much enthusiasm. It seems to the reviewer that a little more restraint in the latter respect would have rendered some of the author's statements more convincing to the reader.

J. N.

BOOKS RECEIVED.

New Books.

Abstracts—Proceedings of the New York Pathological Society, 1927. Pp. 39; 2 illustrations.

*Bronchial Asthma.** By HARRY L. ALEXANDER, A.B., M.D. Pp. 171; 8 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $2.25.

*A Text-book of Surgery.** By W. WAYNE BABCOCK, M.D., F.A.C.S. Pp. 1367; 1050 illustrations, 9 in colors. Philadelphia: W. B. Saunders Company, 1928. Price, $10.00.

*Surgical Diagnosis in Tabular Outline.** By A. J. CEMACH. Translated by EDWARD L. BORTZ, M.D. 109 tabular forms and 129 plates with 548 subjects. Philadelphia: F. A. Davis Company, 1928. Price, $12.00.

* Reviews of titles followed by an asterisk will appear in a later number.

Guy's Hospital Reports, Volume 78 (Volume VIII, Fourth Series), No. 3, July, 1928. Pp. 125. London: Lancet Limited, 1928.

*Practical Surgery of the Abdomen.** By GEORGE H. JUILLY, M.D. Pp. 1275; 1291 illustrations. 2 volumes. Philadelphia: F. A. Davis Company, 1928. Price, $16.00.

*Epilepsy.** By WILLIAM G. LENNOX and STANLEY COBB, M.D. Medicine Monograph No. XIV. Pp. 197; 14 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $3.50.

Medical Clinics of North America (Chicago Number—July, 1928). Pp. 290; 54 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Progressive Medicine, Volume III. Edited by HOBART AMORY HARE, M.D. September, 1928. Pp. 304, illustrated. Philadelphia: Lea & Febiger, 1928.

*Experimental Pharmacology.** By TORALD SOLLMANN, M.D. and PAUL J. HANZLIK, M.D. Pp. 321; 36 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $4.25.

Surgical Clinics of North America, Volume VIII, No. 4 (Philadelphia number, August 1928). Pp. 285; 91 illustrations. Philadelphia: W. B. Saunders Company, 1928.

United Fruit Company—Medical Department. Sixteenth Annual Report, 1927. Pp. 368; illustrated. Boston: United Fruit Company, 1928.

New Editions.

Preventive Medicine. By MARK F. BOYD, M.D., C.P.H. Third edition. Pp. 475; 151 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $4.50. Covering the usual topics in a concise but far from exhaustive manner.

*The Determination of Hydrogen Ions.** By WILLIAM MANSFIELD CLARK, M.D. Third edition. Pp. 717; 103 illustrations. Baltimore: Williams & Wilkins Company, 1928. Price, $6.50.

Diseases of the Ear, Nose and Throat. By WENDELL CHRISTOPHER PHILLIPS, M.D. Seventh edition. Pp. 922; 615 illustrations. Philadelphia: F. A. Davis Company, 1928. Price, $9.00. Apparently a careful effort to keep this work "abreast of the subject."

*The Heart in Modern Practice.** By WILLIAM DUNCAN REID, A.B., M.D. Second edition. Pp. 466; 81 illustrations. Philadelphia: J. B. Lippincott Company, 1928. Price, $6.00.

*A Textbook of Fractures and Dislocations.** By KELLOGG SPEED, S.B., M.D., F.A.C.S. Second edition. Pp. 952; 977 illustrations. Philadelphia: Lea & Febiger, 1928. Price, $11.00.

Stedman's Medical Dictionary. By THOMAS LATHROP STEDMAN, A.M., M.D. Tenth edition. Pp. 1148; illustrated. New York: William Wood & Co., 1928. Price, $7.50. Five hundred new medical terms have been added and many others changed or dropped, necessitating an increase of 200 pages since the first edition. The customary heterogeneous tables are found as appendices. A trustworthy desk helper.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Interpretation of Gastric Symptoms.—BOLTON (*Lancet*, 1928, cciv, 1211) was a recent presenter of the Croonian Lectures, taking as his subject "Interpretation of Gastric Symptoms." One of the interesting features of his three papers that appear is the new division of the clinical phenomenon of gastric disorders into three main syndromes. He describes the symptoms of these syndromes as follows:

"*Pyloric Syndrome.* Pain appearing in the pyloric area during the later stages of digestion. It is accompanied by secondary cardiac symptoms, either an empty hungry feeling, or a sensation of fullness, or of pain. Vomiting occurs with pain in a certain number of cases. Pyloric pain may be absent and secondary cardiac symptoms may alone be present. In all the types of cases acid eructations and secondary esophageal symptoms commonly occur. The symptoms in all cases are relieved by food.

"*Cardiac Syndrome.* Pain, or fullness only, appearing in the cardiac area during the early stages of digestion, or moderately late, or irregularly. Vomiting occurs with pain in a certain number of cases. Secondary esophageal symptoms are common, and the fluid eructated is more likely to be bitter or neutral than acid. The symptoms may, or may not, be relieved by food.

"*Esophageal Syndrome.* This is either primary or secondary and consist of pain, or one of the minor sensations, in the esophageal area. The upper and lower parts of the esophagus differ, in that the symptoms affecting the latter show, to a considerable extent, similar time relations to food as the body of the stomach; whereas, in the case of the former

the symptoms characteristically appear quite early or irregularly. The symptoms of the lower part may or may not be relieved by food, but the relief afforded to those of the upper part is usually only temporary or partial. Vomiting may occur from regurgitation of fluid, which is of the same nature as that of the cardiac syndrome."

Sur l'Inconstance de l'Intradermo-réaction Cholestérinée au Cours des Affections Hépatiques et Particulierement de la Lithiase.—The authors, LOEPER, BINET and LEMAIRE (*Presse méd.*, 1928, **53**, 833) first call attention to the apparent relationship of acute and biliary lithiasis. They have attempted to study this relationship by injecting a small amount of cholesterinized iron into the skin. In a certain number of cases, they have gotten positive results; in a larger number of cases, intradermal tests have been negative. They conclude, naturally, that this test is of little value as a diagnostic aid in conditions in which the possibility of the presence of gall stones has to be considered diagnostically.

The Clinical Recognition and Physical Signs of Bundle-branch Block.—Bundle-branch blocks is appreciated nowadays as not a rarity but an extremely common condition. It has been recognized largely, in fact almost entirely, by the electrocardiographer. Naturally, there is the desire on the part of the clinician to recognize clinically all the various types of cardiac arhythmia. One by one we are learning to observe, through our clinical senses that there are certain fairly distinct signs of different kinds of arrhythmias. This has not been so in the case of bundle-branch block. The trio of physical findings which has enabled KING (*Am. Heart J.*, 1928, **3**, 505) and his coworkers to make a diagnosis of bundle-branch block correctly in a fair number of cases are: (1) Visible bifid apex thrust; (2) palpable bifid apex thrust; (3) feeble heart sounds, with a sound and an asynchronous murmur accompanying the two elements of the systolic thrust.

The Serum Treatment of Erysipelas.—MCCANN (*J. Am. Med. Assn.* 1928, **91**, 78) discusses the evidence that has been brought forth so far as to the efficacy of the present serum which is being used to a large extent throughout the country in the treatment of this specific disease. He concludes that the value of the serum treatment has not been established nor will it be established until analysis has been made of a long series of cases, with simultaneous controls of untreated patients, so that the factors of age, sex, seasonal and annual variations may be contrasted. Previously published reports are of little value because of the lack of controls. From the small series of cases that he has observed he believes that, as a matter of fact, from a comparison with the statistics of previous years, the duration of stay in the hospital and the mortality rate are worse in serum treated patients than in the untreated patients he observed before the serum came into use.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

The Distal Anterior Closed Space Infection.—CARP (*Surg., Gynec. and Obst.*, 1928, **46**, 484) says that for many years Kanavel and Auchincloss have stimulated assistants and students to a better understanding of hand infections. The distal anterior closed space is a confined small compartment on the volar surface of the finger. It extends from the distal crease to the tip. The infection as observed in a general hospital occurs most frequently in the second, third and fourth decades and is about equally divided between the sexes. A puncture is the most important etiologic factor. The hemolytic Staphylococcus aureus is the chief infecting organism. Local tenderness is the most important sign. Complications depend upon direct extension and lymphatic drainage. The treatment is surgical and it is based upon the unique anatomy of the distal anterior closed space. Diseased bone demonstrated clinically and by the Roentgen ray does not necessarily sequestrate, especially if adequate surgical drainage has been obtained. A line of demarcation in dead bone is the indication for sequestrotomy. Cutting away or curettage of dead bone is contraindicated. Removal of drains after about forty-eight hours is preferable. The average period of disability is about three weeks. In cases treated early and well the end results are good. An epithelial cleft, clubbing and stubbing of the finger, incurvation of the nail, sensory disturbance and loss of substance may result.

Partial Obstruction of the Ureter.—SMITH and OCKERBLOD (*J. Urology*, 1928, **19**, 347) state that partial obstruction of the ureter causes an entirely different series of abnormal changes from those resulting from complete obstruction of the tube. It was noted that damage to the ureter does not occur experimentally apart from serious changes in the kidney, pelvis and parenchyma. The ureteral damage is in direct relation to the point of obstruction, the nearer the bladder the greater the ureteral tortuosity and redundance. The kidney pelvis in a partially obstructed ureter may obstruct the vena cava as it did in one of the cases, and also this enlarging kidney pelvis may so put on a stretch bloodvessels, which were in the beginning normal, that they may become the so-called aberrant vessels. So that in this respect a dilatation of the kidney pelvis or ureter may produce an aberrant vessel, as well as an aberrant vessel may produce obstruction to the ureter. Fibrous bands which form may become permanent adhesions, which may bind the

ureter in its new position, even after the obstruction has been released. Ureteral kinks which have been reckoned by some clinicians, to be causative factors of symptoms attributed to ureteral obstruction, are, according to the present experiments, only a by-product of ureteral obstruction.

The Present Status of Inguinal Hernia and its Repair.—MAXEINER (*Minn. Med.*, 1928, **11**, 279) suggests that recurrent hernia represents the incompletely removed original hernia or the development of an incisional rupture following the breakage of sutures by coughing, vomiting or wound infection. The work of Erdman is especially noteworthy, because of the extreme care used in repeated examinations and the large percentage of his cases which returned for reëxamination. His records show that 47.9 per cent of all recurrences were noted within six months after operation, 73.9 per cent within twelve months and 98.6 per cent within two years. He believes that a case may be considered cured if a recurrence does not take place within two years. Reports of recurrence in hernia according to Watson vary from 1 to 10 per cent.

The Treatment of the Common Injuries of the Corpus.—LITTLE (*Lancet*, 1928, i, 870) says that the mechanism of the wrist is unique among the articulations of the human body. It allows more kinds of movement than any other joint and it takes a great part in the finely coördinated actions which characterize the hand. In the normal wrist many landmarks can be made out by palpation. In a case of recent injury, however, inflammatory swelling generally masks all or most of these points. Any interruption or irregularity of its line of curvature either in an anteroposterior or lateral view is evidence of displacement or fracture of the semilunar or scaphoid, which if not corrected leads to arthritic changes. According to Destot of Lyons fractures of the scaphoid or semilunar, and dislocation of the latter, account for 95 per cent of injuries to the wrist, excluding sprains. The symptoms of sprain of the wrist are familiar and in no essential very different from those of the carpal fracture. Differential diagnosis depends upon a careful study of the Roentgen ray plates. When this provides no evidence of fracture or dislocation, sprain may be assumed by a process of elimination. Simple fractures of the scaphoid are almost invariably caused by falls on the extended hand and fingers, or by violence applied in the same direction. Falls from a great height may cause extrusion of a carpal bone through the skin of the palm. In such cases the forearm bones may also project through the skin. Many experiments have been made on the dead body with various results, but it is impossible in the cadaver to reproduce the conditions present in life, particularly as no artificial substitute can be found for muscular action, which by fixing the joint in a given position must influence the nature of the resulting injury. The semilunar is rarely dislocated and fractured at the same time. In an extensive dislocation impairment is great and permanent from marked ligamentous derangement.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Formation of Antirachitic Vitamin in the Absence of Light.—In a former research SCHITTENHELM and EISLER (*Klin. Wchnschr.*, 1928, **7**, 1118) demonstrated the presence of vitamin D as well as vitamins A, B and E in the first sproutings of barley. In the present study they add the observation that in these sprouts there is no preliminary stage or provitamin that can be activated by light energy. Ultraviolet irradiation did not increase the antirachitic activity. In certain cases in which the irradiation was particularly intense or its action was prolonged a decrease of antirachitic activity was noted. The sprouting of the barley took place in dark rooms, so that all question of an action of light could be excluded. They have not been able to demonstrate ergosterol in the sprouts. Barley itself is inactive. It seems that vitamin D can originate in the process of germination and the antirachitic substance is not dependent on light energy.

Congenital Syphilis.—MCBRIDE (*Arch. Dermat. and Syph.*, 1928, **18**, 79) states that all patients with congenital syphilis, with the exception of some of those with neurosyphilis can be cured. Part of the patients with neurosyphilis can be cured, but when symptoms of paralysis in children have developed he was unable to establish a remission. Sulpharsphenamin in the cases observed by him produced dermatitis more frequently than the other arsphenamin preparations. Intensive treatment at short intervals proved more effective than treatment at long intervals. The treatment that he now gives is for the first day arsphenamin and bismuth, for the third day arsphenamin and for the fifth day arsphenamin and bismuth. This is a convenient method of treatment especially if the patients are drawn from a large area, thus making residence away from home necessary for the duration of the treatment. With the intensive method a cure was effected with approximately 65 per cent of the treatment necessary when the moderate method of treatment was used. The duration of the disease was also decreased, thus diminishing the chance of developing a severe syphilitic complication.

The Treatment of Diphtheria Carriers.—HARVEY (*Lancet*, 1928, ii, 58) investigated several methods of treating diphtheria carriers, and the only satisfactory method that he found was douching the nose with a mildly alkaline nasal douche. This yields excellent results when properly carried out. Tonsillectomy is very satisfactory in those carriers where the organisms are found only in the throat. The ear carrier, which is rare, is very difficult to clear up, and responds to treatment very unsatisfactorily. The treatment of diphtheria carriers should consist of rectifying local abnormalities and pathologic conditions which are the causes of the carrier state. If this is done promptly and properly

the numerous bacteria that are present will be diminished and the diphtheria will also in all probability disappear. Diphtheria carriers should be treated as early during the convalescence as is compatible with safety, as the likelihood of the children developing complications must always be held in mind. The longer the bacilli are allowed to remain in the infected area the more difficult their removal becomes. The loss of time from education and the costs to the community makes the necessity of early treatment additionally important.

Fetal Mortalities.—KAMPERMAN (*Am. J. Obst. and Gynec.*, 1928, **16**, 66) analyzed 2478 births. There were 163 deaths, or a mortality of 6.65 per cent. In 63 cases the fetus was nonviable. There was premature birth in 22 cases. In 27 cases the causes of death were not known. In 33 cases death was due to a nephritic toxemia. Placental bleeding was the cause of death in 18 cases. Eighteen cases succumbed as a result of congenital malformations. Eighteen cases died as a result of difficulties encountered in delivery. There were 11 labor deaths; 5 as a result of prolapse of the cord, 6 neonatal and 4 postmaturity deaths. Only 3 deaths were due to eclampsia.

The Cerebrospinal Fluid of Premature Infant.—GLASER (*Am. J. Dis. Child.*, 1928, **36**, 195) has found that the most frequent cause of unsuccessful lumbar puncture in premature infants is the pushing forward of the loosely attached dura of the posterior wall of the spinal canal by the needle. It will occur much less frequently if the tap is made with the child in an upright position and when a fine hypodermic needle is used. In premature infants if the proper technique is used lumbar puncture is a relatively safe procedure, and is often of the greatest value in the diagnosis and treatment of cerebral hemorrhage. Bloody spinal fluid obtained from these infants is suggestive but not absolutely diagnostic in intracranial hemorrhage. If the blood is due to the trauma of the puncture it usually cannot be differentiated from blood resulting from intracranial hemorrhage. The presence of red blood cells in microscopic numbers in the spinal fluid of premature infants during the early days of their lives is a physiologic phenomenon. The most common form of intracranial hemorrhage in premature infants is the subpial hemorrhage. At times hemorrhage may occur that terminates fatally and grossly or even microscopically there is no blood in spinal fluid. Xanthochromia is a physiologic phenomenon during the first four weeks or so in premature infants. The degree of xanthochromia may conveniently measured quantitatively by means of the icterus index. This index in premature infants is highest during the second week. More than half of the yellow spinal fluids of these infants give a positive indirect van den Bergh reaction. Yellow spinal fluids with a high icterus index may give neither a positive benzidin test nor a positive van den Bergh reaction. This is due to coloration by pigment intermediate between hemoglobin and bilirubin. With a positive direct van den Bergh reaction of the spinal fluid intracranial hemorrhage is strongly suggested. Glaser feels that cerebral hemorrhage contributes to the degree of icterus neonatorum, and unrecognized hemorrhage is the cause of so-called physiologic icterus neonatorum.

A Possible Causal Factor of Food Allergy in Certain Infants.—RATNER (*Am. J. Dis. Child.*, 1928, **36**, 277) in his studies found that the placenta in human beings and in guinea pigs is permeable. Proteins pass from the maternal circulation through the placenta. The human fetus and the fetus of the guinea pig can be actively sensitized *in utero*. Proteins can enter the circulation in an unchanged state from the maternal intestinal tract and thereby gain entrance to the fetal circulation. Therefore under certain conditions an infant with a predisposition for allergy may become actively sensitized *in utero* because of the mother's overindulgence in certain protein foods during her antepartum period, and after birth, when coming in contact with this food for the first time, it will manifest some form of allergic phenomenon. This is the explanation for allergy developing in certain infants.

Prenatal Syphilis.—MARSHALL (*J. Am. Med. Assn.*, 1928, **91**, 702) believes that a marked reduction of fetal and infant mortality can be obtained in syphilitic families by treating the mother during gestation. The earlier this treatment is begun, the greater the probabilities for a normal child developing. Even in recently acquired syphilis the changes for healthy offspring are good with efficient antepartum treatment. Syphilitic mothers should be treated during each pregnancy. The pregnant woman with her defense mechanism at its highest development is more amenable to treatment than the nonpregnant woman or the syphilitic man.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Cultivation of the Microsporon of Malassez.—MACLEOD and DOWLING (*Roy. Soc. Med. Proc., Brit. J. Dermatol.*, 1928, **40**, 246) report the successful cultivation of the microsporon of Malassez from patients with seborrheic affections and the reproduction of the disease in susceptible subjects by the cultivated organism. The experiments were carried out on two classes of patients: (*a*) Those already suffering with seborrheic dermatitis of various types in which the fungus had been recovered from the scrapings; (*b*) patients with normal and with seborrheic skins, who had no seborrheic dermatitis. There was no difficulty in the first group in reproducing, by inoculation, the clinical picture of seborrheic dermatitis in every case. Controls were negative throughout. The

primary reaction after scarification is a group of follicular papules, and after intradermal inoculation a furfuraceous scabbiness. The implanted lesions sometimes extended and merged with the original process. The disease reproduced by inoculation ran a course of three to four weeks. Normal skins reacted within twenty-four hours by the development of a group of follicular papules, and seborrheic subjects developed widespread irritable patches. It is conceded that some as yet unknown alteration of sebaceous and sweat secretion is essential to the development of the seborrheic infection.

Serum Calcium Determination in Cutaneous Disease.—BURGESS (*Brit. J. Dermatol. and Syph.*, 1928, **40**, 279) reviews the literature of serum calcium determination in cutaneous disease, including the work of Klauder and Brown and of Greenbaum in this country. The former it will be recalled found in the rabbit that cutaneous irritability rises with an increase of potassium and a decrease of calcium in the tissue and that the reverse is also true. Greenbaum found that there was no distinctive abnormality of blood calcium associated with urticaria. By determining separately the precipitable calcium and the total (ash) calcium of the serum, as suggested by Vines and Grove, the writer found that precipitable calcium may be markedly reduced while total calcium shows little or no change. As suggested by Pulay, the writer finds that urticaria associated with dermographism tends to a low precipitable serum calcium, while other chronic urticarias do not. His collected results indicate that the large majority of cases of prurigo, alopecia totalis, light sensitization (adult type) and eczema show a similar reduction of precipitable calcium. Reduction also occurs in 50 per cent of cases of acroasphyxia and erythema pernio, in which it has long been known that an almost specific response can be secured in some cases by calcium-parathyroid therapy while others are unaffected. The writer considers that his results support the value of calcium-parathyroid therapy in neurogenous dermatoses and confirm the observations of Klauder and Brown.

Roentgen Ray Treatment of Acne Vulgaris.—MICHAEL (*Arch. Dermat. and Syph.*, 1928, **17**, 604) concludes that no ill effects follow the use of Roentgen ray in moderate dosage by the MacKee system; that recurrences range from 6 to 35 per cent of the treated cases, but are usually safely disposed of by another short course of treatment. The author does not believe it desirable to treat beyond the point of disappearance of lesions, and admits the importance of diet and general measures in individual cases. The older the patient at the time treatment is instituted, the greater the likelihood of cure in a single course (ten treatments). Ultimate permanent success was obtained in 85 per cent of cases, the best result by any method reported.

The Protease of Pathogenic Fungi.—MALLINCKRODT (*Arch. f. Dermat. u. Syph.*, 1928, **154**, 493) reports the isolation of a protease from pathogenic fungi, which, like the trypsin of animals, can be isolated in powder form. It is present both in the growing fungus and in the medium.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Results of Irradiation in Cervical Cancer.—In a report based upon some of the work which has been done in the Howard A. Kelly Hospital in Baltimore, WARD (*Am. J. Roentgenol.*, 1928, **19**, 330) claims that 50 per cent of the operable cases of cancer of the cervix which have been subjected radium irradiation have passed the five-year mark with no evidence of the growth and in addition there has been no primary mortality in the entire series. In 141 inoperable cases 9 per cent were clinically cured when last seen and 4 per cent have passed the five-year period as well. This series of 141 cases represents over 60 per cent of the material reported in this paper and shows that there is still a long way to go before we reach the ideal of getting most of the cases to present themselves for treatment while the disease is still in the early or operable stage.

Treatment of Gonorrhea with Living Gonococci.—In a previous review, we abstracted an article from the German literature in which the injection of living gonococci was advocated in the treatment of gonorrhea in the female. It is of interest therefore, to present the substance of another article from a similar source endorsing such treatment. WOLFF (*Zentralbl. f. Gynäk.*, 1928, **52**, 674) seems to be very enthusiastic about the use of the living gonococcus vaccine in the treatment of the resistant chronic infections. He considers this method a distinct advance in the treatment of the disease as he knows of no other method which has been previously used which will give as good results in such a short time. The great difficulty in the past has been the problem of having a fresh pure culture of gonococcus available at all times. This has now been overcome by the production of a commercial preparation called "Gonovitan" which is merely a pure culture of the gonococcus in ampules. It is potent if used within its expiration date which is marked on the package and is usually from two to three months. The patients usually receive two injections at an interval of from eight to ten days and they remain ambulatory while under treatment.

Report from Belgium on Radiotherapy.—The experiences with radium irradiation in the treatment of carcinoma of the cervix which he has had in his clinic in Brussels have been presented by CHEVAL (*Brit. Med. J.*, 1928, i, 537). Since 1919, he has tried almost every method of application but the best results have been obtained with the method

used since 1926. This method consists of the use of large quantities of radium applied at a distance from the patient. He has constructed an apparatus which contains 4 gm. of radium element and which allows the irradiation of two patients at the same time in large fields. The whole of the small pelvis is irradiated with equal intensity and in spite of the enormous dosage the patient is rendered neither anemic nor shocked. He is of the opinion that radium will cure more than one-half of the operable cases, one-third of the borderline cases and from 10 to 20 per cent of the cases in the inoperable stage and, therefore, should easily supersede surgery.

Referred Pain in Ovarian Cysts.—A rather interesting observation on the diagnostic value of referred pain in cases of ovarian cysts which have undergone torsion has been presented by KOUCKY (*Surg. Clin. North America*, June, 1928, p. 663). He has seen several cases of this type in which pain was present over the upper part of the outer aspect of the thigh on the same side as the tumor. He believes that this pain is undoubtedly a referred one. Twisting of the pedicle of the tumor causes traction on the broad ligament and surrounding peritoneum and the nerve fibers of this peritoneal area are connected with the second lumbar segment which also innervates the upper part of the lateral aspect of the thigh. This pain is often overshadowed by the more severe abdominal pain but direct questioning will usually reveal its presence.

Cervical Fibroids. — One of the rarest types of uterine fibroids, and certainly one of the most difficult conditions in gynecology to properly treat, is the condition known as cervical fibroids, namely, uterine myomata originating in the cervix of the uterus and remaining in that location while increasing in size. In reporting three cases of this type DE SA (*J. Obst. and Gynec., British Empire*, 1928, **35**, 331), of Bombay, states that about 8 per cent of fibroids arise in the cervix. If this statement is correct it is almost certain that a large majority of them do not remain in the cervix, even though arising there since the mature cervical fibroid is comparatively rare. He was very fortunate in operating upon his 3 cases without great difficulty, and in reading his case reports it can be seen that the key to the situation in each case was that the bladder was first separated from the tumor, after which an incision was made in the uterine muscle over the tumor, the tumor was shelled out and then hysterectomy was proceeded with in the usual manner. In all 3 of these cases the tumor involved the anterior portion of the cervix. Had it involved the posterior portion there would have been no advantage in primary separation of the bladder. However, primary enucleation of the tumor is a very helpful procedure because in these cases the normal relationships are so distorted that before the tumor is enucleated hysterectomy would be a considerably more hazardous procedure. In any event, the removal of these tumors is no job for the inexperienced surgeon or casual operator.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Treatment of Certain Diseases of the Eye by Ultraviolet Light.—HUME (*Brit. J. Actinotherapy*, 1928, **3**, 87) uses a mercury-quartz vapor lamp in treatment of diseases of the eyes with good results in some diseases. In herpes zoster irradiation of the affected part of the skin of the forehead, temples and eyelids, carried to the extent of moderate erythema, produced in 5 cases profound relief and permanent disappearance of the disease. Sterilized vaselin over the affected area relieved the irritability later associated with the erythema. During actual irradiation the skin was protected with vanishing cream or olive oil.

Ulcers on the Cornea. The author emphasizes the fact that in directing the rays from the lamp on the cornea care should be taken that the rays be directed in the form of a narrow pencil of light and that they hit the cornea tangentially so as not to penetrate the eye. Injuries to the lens and retina are avoided if one excluded infra red rays by a sulphate or iron filter and a great part of the light rays by a blue-violet uveal glass.

Ulcer Serpens. Loss of the eye in this trouble has been reduced one-fourth since the use of irrigation. The use of light is not indicated in interstitial keratitis until the period when the peripheral margins of the cornea show a definite resolution of the cloudy surface. In phlyctenular keratitis the progress exhibited by the affected child after localized and generalized radiation is remarkable. The author states that in only 10 per cent of the cases was it necessary to evert the lids and radiate the palpebral conjunctiva directly. The consensus of opinion is that it is possible to cure 10 per cent of the cases of trachoma and to improve 80 per cent, 10 per cent not being improved. The conjunctiva is irradiated by everting the lids, exposing them at a distance of $\frac{1}{2}$ meter to the full force of the whole length of the spectrum of the mercury-vapor lamp for at least fifteen to twenty minutes. After a few days a slough separates from the conjunctiva at the site of the exposure. It is not desirable to use this treatment more than once, and then only in the severest cases. Vernal catarrh was influenced favorably by ultraviolet irradiation but inferior to radium. The author uses ultraviolet irradiation in myopia to delay the progress in childhood by increasing the calcium content of the blood.

Seasonal Changes in the Frequency of Phlyctenular Eye Diseases and Trachoma.—WERNER (*Acta Ophthal.*, 1928, **6**, 132) studied the records from 1912 to 1926 in the Helsingfors Ophthalmic Hospital and concluded that the frequency of the phlyctenular eye diseases in

Finland is subject to seasonal changes in such a manner, that the number of cases increases toward the spring, after the long winter, and decreases during the summer and autumn. The favorable effects of the summer make themselves felt right up to February of the following year. This corresponds, on the whole, to the seasonable variations in tuberculosis. The frequency of trachoma on the other hand, is not subjected to seasonal variations.

Juvenile Atrophy of the Optic Nerve.—Lamb (*J. Missouri State Med. Assn.*, 1928, **25**, 415) states that of 559 pupils in attendance at the Missouri School for the Blind during the last twenty-three years, 84, or 15 per cent, have lost their sight from optic atrophy. Only those cases are included where visual disturbances occurred under twenty years of age. No case of Leber's hereditary optic atrophy was found. Those below twenty years of age were 73 cases in all, 55 per cent of which were boys and 33 per cent were girls. As to the cause, 10 of the 73 cases were due to meningitis, 3 were due to brain tumor, 2 to typhoid fever, 1 to scarlet fever, 1 to tower skull and 1 to pupura hemorrhagica. In the remaining 53 cases no cause was given. Wassermann tests made in but 38 of the 73 cases resulted in 8 with +4 and 1 with +2 reaction. The author gives statistics of optic atrophy found in other institutions. In 10 blind schools in this country 17.5 per cent of the inmates had optic atrophy. The author thinks there can be little doubt that the 44 cases of uncertain origin in his group were due to congenital syphilis.

Hypertension and the Eye.—Pick (*Deutsch. med. Wchnschr.*, 1928, **54**, 1284) reports the eye changes seen as a result of hypertension are: (1) Arterial changes: (*a*) Silver-wire arteries, narrowing; (*b*) a general uniform contraction of all the retinal arteries; (*c*) arterial-wall changes—variations in caliber to complete occlusion and conversion into white streaks; (*d*) copper-wire arteries. (2) Veins: Dilatation and tortuosity especially of the finer branches. (3) Hemorrhages, white patches in retina, hemorrhages in vitreous, thrombosis of vessels. (4) Sclerosis of the choroidal arteries (Köppe type). In 122 vascular cases there were: (*a*) 89 cases of hypertension with retinal change, (*b*) 25 cases of hypertension without retinal change and (*c*) 8 cases of retinal changes without hypertension, 6 arteriosclerotic, 1 ophthalmic migraine and 1 thrombosis in a chlorotic girl. Of these patients, 3 were under forty years of age, 46 were between forty and sixty years, 34 between sixty and seventy years and 6 over seventy years. There were 13 cases of diabetic retinitis, 2 of which had normal blood pressure, while 10 had normal retinal arteries. In the 89 cases of (*a*) there were vessel changes only in 35, hemorrhage and exudates with vessel changes in 41 and retinal changes without demonstrable vessel changes in 13. Sclerosis of the choroidal arteries of the Köppe type and the uniform general harrowing of the retinal arteries are characteristic of essential hypertension. Arteriosclerotic changes in the fundus, while not necessarily of hypertension origin, are ten times as frequent in the presence of hypertension as without it.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Muscular Attachments of the Tonsil.—Following a discussion of the embryologic and anatomic aspects of tonsils, FOWLER and TODD (*J. Am. Med. Assn.*, 1928, **90**, 1610) conclude: (1) That to place tonsil surgery on a basis of scientific accuracy, it is requisite that the structures involved be fundamentally correct. These structures are complicated, not only the tonsil but the pharyngeal fascia and related muscles: (2) that the tonsil itself is a lymphoid-lined pocket; (3) that the upper lobe is a hood and the lower lobe is a pocket; (4) that the so-called capsule is a thin sheet of fibrous tissue left covering the tonsil after removal—in fact it is a surgical artefact; (5) that the superior constrictor muscle is not an immediate relation, as the palatopharyngeus lies between it and the "capsule," to which it is attached at the groove between the upper and lower pockets by a bundle of fibers, which they call the "tonsillopharyngeus muscle;" (6) that if this muscular attachment is teased through, complete enucleation of the tonsil can be carried out easily and without injury to the underlying structures.

The Pharyngeal Tonsil.—In a communication summarizing the observations of a research on the embryology, bacteriology and pathology of the pharyngeal tonsil, COOKE (*Am. J. Dis. Child.*, 1928, **35**, 229) traces the development of the adenoid from its incipiency at about the fourth month of fetal life to its completion in infancy. Although many functions have been ascribed to the pharyngeal tonsil—protective, internal secretory, hemopoietic, elimination and the production of immunity—there is no reason to believe that the lymphoid tissue of the adenoid differs from that in other parts of the body and it is suggested that its only special object is to function as a surface filter for inspired air, and as a first line of defense. Bacteriologic examinations revealed the presence of well-known common bacteria, and an absence of tubercle bacilli. The condition which attracts attention and invites surgical intervention is hypertrophy, which is discussed along with other pathologic states, including fibrosis, periarteritis and endarteritis in the capsule, and cystic and abscess formation. The author concludes by stating that "hypertrophy of Luschka's tonsil is an important pathologic state, fraught with such immediate and remote dangers that it is a national duty to place the sufferer under skilled supervision at the earliest moment."

The Incidence of Tuberculous Infection in the Faucial and Pharyngeal Tonsils of Children.—With a view of ascertaining whether the high percentage of tuberculous tonsils (9 per cent) found by Mitchell, in Edinburgh, in cases with enlarged tonsils without obvious tuberculous

adenitis continued to be found in normal postwar conditions and in other parts of Britain, SCARFF and WHITBY (*J. Laryngol. and Otol.*, 1928, **43**, 328) investigated the tonsils in 100 cases by histologic methods only, and the tonsils and adenoids in a further 100 cases both by histologic methods and by animal experiment. The materials were obtained at the Middlesex Hospital from children of ages ranging from two to twelve years. Of the first group, only 2 were found to show tubercle formation; and in the second group, only 3 yielded evidence of tuberculosis, either by histologic examination, animal inoculation, or both. These results are similar to those reported from the University of Michigan by Weller (2.35 per cent). The authors believe that improvement in milk supply can account for the decrease in the incidence of tonsillar tuberculosis and that tonsillectomy in tuberculous cervical adenitis is a justifiable procedure.

In the same issue two interesting case reports of tuberculosis of the tonsil appear—one by MURRAY and MAXWELL, page 335; and the other by HORGAN, page 338.

RADIOLOGY

UNDER THE CHARGE OF

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Nonopaque Foreign Bodies in the Air Passages.—According to ALLISON and PHELPS (*Radiology*, 1928, **10**, 157) the clinical features produced by a nonopaque foreign body in the air passages are very striking and quite different from those due to a metallic foreign body. The outstanding feature is the violence of the reaction; the peanut, which is the most common, seems also to be the most toxic. The reaction consists of trauma, edema, congestion, exudation, spasm and toxemia. Two years or younger is the age of the patient in 90 per cent of the cases. As a rule, the younger the child the more serious the reaction. The history to be obtained from the mother is of the greatest importance; when she tells of her baby choking on something and "swallowing it the wrong way," she is right in 96 per cent of the cases. The Roentgen signs, described by Manges, Jackson and others, include (1) unilateral emphysema on the affected side, (2) flattening and limited mobility of the diaphragm on the affected side, and (3) displacement of the heart and mediastinum toward the unaffected side. These signs are all best elicited on films made following complete expiration. The above mentioned signs were present and diagnostic in 22 of 26 cases seen by the authors. In no case was there evidence of atelectasis, drowned lung or abscess formation, probably because the cases were seen early and the

obstruction was not complete. In every instance except 2, the foreign body was found with the bronchoscope either in the indicated bronchus or the trachea. In 2 cases, no foreign body was found, but the patients recovered after bronchoscopic exploration and the obstruction was doubtless due to a plug of mucus. In the remaining 4 cases the Roentgen examination was negative but a foreign body was found in the trachea with the bronchoscope.

Pancreatic Lithiasis.—SEEGER (*Radiology*, 1928, **10**, 126) has found in the literature reports of 26 cases in which pancreatic calculi were removed at operation, and adds 1 of his own. Pain is the most important symptom and is variable in character. It is usually epigastric, and may be dull, continued or intermittent, or occur in colics like those produced by gall stones. Radiation to the left is regarded as characteristic but rarely occurred in the cases recorded. Glycosuria, when present, occurs only in advanced stages of the condition and is then due to the associated interlobular pancreatitis. On the whole, clinical diagnosis is difficult if not impossible and was made before operation in only 2 of the 26 cases. In several instances Roentgen-ray examination revealed shadows of the stones.

Discussing this report, Kirklin said that he had been able to find only 2 cases at the Mayo Clinic in which there was roentgenologic evidence of the condition. In the first, a case of multiple stones in an accessory pancreas, there was a blotchy mass of shadows just to the right of the first lumbar vertebra. In the second case, the shadows were at the level and partly in front of the second lumbar vertebra. Case, of Battle Creek, said that he had had 5 cases. In 1 instance, the shadows of the stones completely outlined the pancreas.

Five Year End Results of Radium Treatment in Carcinoma of the Cervix Uteri.—In a series of 227 cases of carcinoma of the cervix treated by POMEROY (*Am. J. Roent. and Rad. Ther.*, 1928, **18**, 514) 29, microscopically proved, have been observed five years or longer. Of these 29 cases, representing all grades of severity, 5 or 17.24 per cent are apparently well. Tumors classified as adenocarcinoma of the cervix constitute over half of these apparently arrested cases. Four of the 5 arrested cases were treated by radium alone. In the fifth case Roentgen radiation was used in addition to radium.

Scientific Basis of Phototherapy.—After discussing the physics of phototherapy, GRIFFITH and TAYLOR (*Radiology*, 1928, **10**, 93) cite its applications in disease. Ultraviolet radiation of foodstuffs and patients has proved highly effective in rickets, and its beneficial effect in tuberculosis is well known. During the past eighteen months, the writers have treated a large number of cases of pulmonary and surgical tuberculosis with improvement in a high percentage. The authors stress the remarkable general response of practically all tuberculous patients, both pulmonary and extrapulmonary, to ultraviolet treatment. With the advent of heliotherapy reinforced by artificial light therapy, the tendency to introspection and pessimism was replaced by a high optimism, and the patients became bright and cheerful. For the last six months, irradiation has been practised on acute lobar and bronchial

pneumonias, immediately after the crisis had occurred or immediately after the temperature had settled. In the case of children suffering from whooping cough, without any pneumonic complications, ultraviolet irradiation has been practised from the day of admission, apparently with much benefit. Pneumonias seem to be making a more rapid convalescence under ultraviolet therapy. The method is also being tried in diphtheria.

Cholecystographic Studies after the Administration of some of the Popular Cholagogues.—It is generally believed that the commonly used cholagogues not only increase the secretory activity of the liver but at the same time cause an increase in the flow of bile by an actual emptying of the gall bladder. To determine the facts, STEWART and RYAN (*Am. J. Roent. and Rad. Therap.*, 1928, **19**, 341) have tested 14 drugs of this class. The procedure consisted in administering the sodium salt of tetraiodophenolphthalein as usual for cholecystography. The gall bladder shadow obtained sixteen hours later was used for comparison, for at this time maximum concentration has been reached. The drugs were given after the sixteen-hour observation, and frequent examinations were made from one-half to eight hours after. The cholagogues used were calomel, sodium salicylate, sal cathartic, sodium phosphate, Seidlitz powder, hydrochloric acid, podophyllin, pituitrin, bile salts, oleic acid, olive oil, olive oil emulsion, castor oil, cod-liver oil emulsion. Of all the drugs used, oleic acid caused the most marked response; in 1 case the gall bladder emptied completely in three hours. Olive oil pure or emulsified showed some emptying power. With the exception of oleic acid none of the drugs used caused as great or as rapid emptying as a simple meal. Singularly enough this fact was stated by Naunyn in 1892. The act of digestion is the necessary factor in emptying the gall bladder. No reaction whatever was obtained from castor oil, sodium salicylate, bile salts, salcathartic, Seidlitz powder or sodium phosphate. When podophyllin and hydrochloric acid were given the bile content was apparently increased. Calomel and pituitrin, although not causing emptying, appeared to excite the gall bladder to activity as indicated by changes in size, form and concentration. In some of the patients an actual peristalsis was suggested.

Physiologic Action of Diathermy in Pneumonia.—In lobar pneumonia, according to CLEMENT (*Arch. Phys. Ther., X-ray, Rad.*, 1928, **9**, 199), diathermy maintains the stage of congestion, prevents the morbid process from progressing to the stage of red hepatization or gray hepatization and afterward relieves the congestion. It favors phagocytosis by hindering bacterial activity. It promotes lung aëration as is proven by the rapidity with which cyanosis disappears. There is a relaxation of the tension on the tissues surrounding the pneumonic solidification. The bloodvessels dilate near, but not in the inflammatory area. The carrying capacity of the arteries and veins is increased. This means more blood flowing to and from the inflamed part. It results in local heat dispersion and an equalization of the interchange of pressure between the vessels and the surrounding tissue. Consequently congestion never becomes stasis. Red hepatization never becomes purulent. Redness disappears when congestion ceases. The temperature falls

by lysis. Convalescence is markedly shortened. The effect of diathermy upon the patient's feeling is gratifying. He is quite promptly relieved of his pain, shortness of breath, cyanosis and restlessness. During 1927, out of 88 patients with uncomplicated lobar pneumonia treated at St. Luke's Hospital, Duluth, within forty-eight hours of the onset of the disease, none has died. The total number treated is 94 and the total number of deaths is 6. In these 6 patients treatment was either started late, or the patient was aged, or there were severe complications. The average death rate for all cases is about 6.4 per cent. The average mortality of patients not treated with diathermy is about 20 per cent, and has been as high as 35 to 50 per cent. In the treatment of pneumonia patients as large an electrode as possible is used both in front and behind. An electrode which does not cover more than the area of the consolidation, as outlined by percussion on the outside of the chest, is not large enough. Tissues outside of the area of inflammation must be included in the region through which the current passes. High voltage and comparative low milliampèrage are used. The treatments are given twice daily and are of thirty to forty-five minutes' duration. An average of 6½ treatments per patient are given. The average duration of the treatments is thirty-five minutes. The average milliampèrage, including the treatments given to children, is 1100.

Clinical Evidences of Thyrotoxic Control after Radium Therapy.—Results in a large series of cases were canvassed by LOUCKS (*Am. J. Roent. and Rad. Therap.*, 1928, **18**, 509) to determine whether radium treatment of thyrotoxicosis is efficient. He concludes that the control of symptoms, reduction in size of the gland, increase in body weight and restoration of normal metabolism are sufficient evidence to convince the most skeptical of the merits of radium therapy. Usually tremor is the first symptom to subside after treatment. The improvement is gradual and is noticed in six weeks; after four months tremor of hands or limbs is seldom seen. A gradual increase in weight is the best assurance of control of the toxic condition. Sweating, loss of hair and trophic changes show gradual improvement. Reduction in size of the thyroid gland is in direct relation to the amount of glandular hyperplasia, and more time is required to reduce a cystic adenoma than a simple hyperplasia. A guarded prognosis should be given as to exophthalmos, but cases of less than two years' duration improve. High systolic and low diastolic blood pressure improve in two or three months. Tachycardia, fibrillation and general cardiac disturbances improve slowly but certainly. Improvement in the metabolic rate, which may return to normal in six months, is the most convincing factor.

Abdominal Aneurysm.—Not infrequently the clinician requests assistance from the Roentgen ray in cases of suspected abdominal aneurysm, but since an aneurysm is likely to have virtually the same density as the abdominal structures direct roentgenologic evidence is hard to obtain. However, FARMER (*Am. J. Roent. and Rad. Therap.*, 1928, **18**, 550) reports 2 cases in which there were definite Roentgen signs and a third in which more thorough examination might have revealed such signs. In the first case the aneurysm was seated just below the diaphragm;

the shadow of the mass contrasted with the transparent gas bubble and was pulsatile; the bodies of the twelfth dorsal and first and second lumbar vertebræ were deeply eroded. In the second case the walls of the aneurysm were calcified and distinctly visible roentgenoscopically. In the third case the examination was negative, but Farmer is of the opinion that the aneurysm could have been revealed by pneumoperitoneum; air injected into the colon might also have furnished sufficient contrast. Although new growths also erode the vertebræ, Farmer calls attention to the fact that in his case of aneurysm a crescent-shaped area was destroyed in each of three vertebræ, the intervertebral disks remaining intact, whereas, in a case of benign tumor the disks also were eroded, and a single extensive concavity resulted; this may perhaps be a point in differential diagnosis. At all events, the cases reported indicate that Roentgen examination for abdominal aneurysm is not necessarily futile.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Relation between Brain and Liver Weights in Epilepsy Considered from the Standpoint of Onset and Duration in about Two Hundred Cases.—PATTERSON and WEINGREW (*Psychiat. Quart.*, 1928, **2**, 171) present an analysis of findings postmortem in a group of carefully selected cases. The results are as follows: (1) The general average brain weight of the group falls within the lower limits of the normal range. (2) The general average liver weight of the group is below the accepted normal minimum. (3) In regard to the onset of the disease the brain weight increases progressively with delay in onset, while the liver weight also increases similarly up to the time of its full development, after which there is a gradual but definite decline. (4) With regard to duration of the malady, the brain shows a continuous reduction in weight as the disease progresses, while the liver diminishes steadily in weight up to a certain period and then shows an uninterrupted increase.

Myasthenia Gravis.—NIELSEN and ROTH (*Jour. Nerv. and Ment. Dis.*, 1928, **67**, 32) present 3 cases. "Case I presented poorly developed musculature in general, with evidence of involvement of the bowels, history of sexual excesses and severe psychic trauma. Case II presented history of pregnancy just completed, very low basal metab-

olic rate (−36), with evidence of myxedema, and of vegetative imbalance with involvement of the bowel. Case III presented poor musculature and evidence that practically constituted a diagnosis of syphilis of the central nervous system. Yet all 3 cases had the typical onset and the typical development of myasthenia gravis. All 3 presented the myasthenic reaction of Jolly." The authors observe that it is necessary to discriminate between coincidence and causation. They conclude that the disease seems to occur in persons with small or flabby musculature in general; that the bowels are weakened in the disease just as is the general musculature; that the myasthenic reaction of Jolly is not necessarily present in all muscles at any time and may be entirely absent during remissions; that strychnin has little if any influence on the course of the disease; that the basal metabolic rate is normal; that the origin of the exhaustion is probably neuromuscular.

Bemerkungen zu den mechanisch diagnostischen Methoden in der Chirurgie des Zentralnervensystems.—KRAUS (*Der Nerven.*, 1928, **4**, 215) remarks on the difficulties encountered in ventricular puncture and the after effects of this method. He reports a case of fatal outcome. He then comments on the various methods of encephalography with special attention to the iodipin-lipiodol method and reports a case. The chief interest in this paper is the report on arterial encephalography developed by Moniz and reported by him before the Academy of Medicine in Paris, July 12, 1927. Beautiful pictures of the arterial tree are obtained by injecting 5 cc. of 25 per cent sodium iodid solution into the internal carotid artery. A temporary ligature is placed about the artery prior to injection and drawn immediately. The exposure is made at the moment of injection. Tumors, aneurysms, and so forth, are indicated by distortions of the picture of the arterial tree obtained.

Experiences with Encephalography via the Lumbar Route.—FRIEDMAN, SNOW and KASANIN (*Arch. Neurol. and Psychiat.*, 1928, **19**, 762) report observations made in 47 cases. The technique was simple. Fasting patients were given a hypodermic injection of morphin, $\frac{1}{6}$ gr., and scopolamin, $\frac{1}{200}$ gr. Spinal puncture was performed in the sitting position, 10 to 20 cc. of fluid withdrawn at a time and an equal amount of air injected. An average of from 90 to 120 cc. of air was used. As much as 175 cc. was injected in 1 case and in 1 case satisfactory roentgenograms were obtained with as little as 15 cc. The symptoms observed during the procedure were considered due to the injection of air rather than to the removal of fluid. These were chiefly occipital pain, headache in the frontal region, occasional collapse with pallor and profuse perspiration. At first the pulse is accelerated; later there is bradycardia. At times nausea and vomiting occurred. The after effects were headache, succussion sensations, dizziness and occasionally a meningeal syndrome. In 1 case there was a polynucleosis of 19,500. Death occurred in 1 case only that had fever prior to the air injection. Encephalograms were made immediately after injection and on the following day. On the second day a change is usually noted in the shape of the anterior horns. In 3 cases, though a sufficient quantity of air had been injected, the absence of ventricular air shadows was noted. The clinical material consisted mostly of brain tumor cases

and cases of epilepsy. Altogether, 16 varieties of organic brain disease were studied. Nineteen of the cases are presented in some detail, and encephalograms of typical conditions encountered are used for illustrations. The authors consider the method of value in the localization of tumors; in the differentiation of vascular from neoplastic processes; in traumatic cases, and in excluding hysteria and encephalitis. The procedure was carried out unwittingly in 2 cases of subtentorial growth without deleterious results, although the authors advise against its use in such cases. They describe a condition which they call retracted brain in patients with late epilepsy. They conclude that the endolumbar route has advantages over the trephine insufflation in that it can be carried out by a neurologist in the hospital ward; that the difficulty of finding dislocated ventricles is avoided; that the brain is not traversed in the procedure; the cerebral subarachnoid space and the cisterns are filled with air; that all of the air finds its way into the cerebral spaces, whereas with the Dandy method the air often escapes beside the needle; that this procedure is much safer. They advise against its use in tumors of the posterior fossa and for the demonstration of obstructive internal hydrocephalus.

Psychosomatische Betrachtungen zur Aetiologie und Therapie des Asthma Bronchiale.—NIEDEBURG (*Der Nerven.*, 1928, **2**, 326) calls attention to the marked interest manifested in the literature by the great increase of articles dealing with asthma. He notes the wide divergence of opinion regarding its cause and its treatment. He states that one can differentiate from the clinical standpoint an asthmatic attack (asthmaanfall) from the so-called status asthmaticus, the latter being merely a mild respiratory impediment of an asthmatic nature which may exist for years without attracting special attention. The reversal of the normal respiratory pause is not so sharply marked as in the asthmatic attack, but some of the respiratory characteristics are present. He does not believe that one can differentiate a secretory form from a spasm form of asthma and considers that the status asthmaticus is simply a condition of preparation for attacks. The sputum in both cases contains Charcot-Leyden crystals, Curschmann's spirals and eosinophilic cells. As primary factors in the etiology he mentions changes in the mucous membrane due to severe colds, constitutional factors, which make one especially liable, allergic phenomena specifically of the nature of sensitization and psychological factors in the nature of an habitual response. He speaks of the vicious circle of the asthmatic phenomena. One recalls earlier asthmatic attacks and remembers the distress caused by them, so that one waits with anxiety for the next attack. The bronchitic condition brings about a wish to lessen the impediment to breathing. Forced expiration and expectoration irritates the mucous membrane still more, and this continues until another asthmatic attack is brought about. The author believes the asthmatic condition to be a disturbance of the vegetative functions and, therefore, related to urticaria, Quincke's edema, cardiospasm and pylorospasm, migrain, epilepsy, and so forth. While there are psychic features, he considers it a gross error to treat asthma as if it were a purely psychic condition, and in this connection calls attention to its rarity in neurotic and hysterical individuals. As to treatment, he gives, first, prophylaxis

in the nature of proper breathing exercises and strengthening of the physical and psychic resistances in predisposed individuals as early in life as possible. Also, the early and proper treatment of colds. From the allergic side, desensitization to specific substances to which the individual may be sensitive. Proper breathing habits may be brought about if necessary by the aid of hypnotism. General psychotherapeutic measures to relieve the patient from preoccupation with his condition are indicated in all cases.

PATHOLOGY AND BACTERIOLOGY

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Streptococci from Scarlet Fever and Surgical Infections.—In a study of streptococci KINSELLA, GARCIA and WADE (*Proc. Soc. Exper. Biol. and Med.*, 1927, **24**, 889) question if the criteria used are sufficient to determine the specific nature of a hemolytic streptococcus; the resistance to heating of a filtrate prepared from special culture media; the capacity of such to produce a dermal reaction in a susceptible subject and its neutralization by antiscarlet fever serum in skin tests. They suggest that the phase of reactivity of the patient may determine whether scarlet fever or some other clinical picture will follow a hemolytic streptococcus infection. Three cases of scarlet fever (2 from wounds) and 3 of postoperative bacteremia were studied. From the throats of 2 of the scarlet fever patients only nonhemolytic streptococci were grown and filtrates from these gave the above criteria. In the bacteremia cases (2 mastoiditis and 1 of hemorrhoids) the filtrates of the cultures from the blood also gave these criteria. The meaning of these findings will require further studies.

The Etiology and Pathology of Pyelitis Cystica, Ureteritis Cystica, and Cystitis Cystica.—Cysts of the mucous membrane of the renal pelvis, ureters and urinary bladder have been recognized since the first pathologic description of them by Morgagni in 1761. Although commonly occurring, they rarely give rise to clinical manifestations. MORSE (*Am. J. Path.*, 1928, **4**, 33) observed 125 cases at necropsy and only 3 were recognized macroscopically as pyelitis cystica, ureteritis cystica and cystitis cystica. Sections were made in 100 of these cases from each renal pelvis and from the fundus and trigone of the bladder. The average age was forty-four years. In 108 of the 125, the epithelial buds or cell nests of von Brunn or cysts were found. Evidences of inflammation were found in 58 per cent of these. Serial sections were made at

different levels in 15 cases and Aschoff was confirmed in his opinion that there was no duct connection between the cysts and the lumen. The author arrived at the following conclusions: (1) Glandular structures are not normally found in the urinary tract above the trigone of the bladder; (2) epithelial buds, cell nests, and cysts are not normally found in the urinary tract; (3) cysts of the urinary tract are formed from the epithelial cell nests of von Brunn; (4) the epithelial buds and cell nests are inflammatory in nature; (5) microscopically they are present in most people over twenty years of age; (6) there was no evidence to support the secretory theory of the cyst formation; (7) the cysts are formed by degeneration of the central cells of the epithelial nests.

The Treatment of Typhoid Carriers.—Many attempts have been made to discover substances which when injected into the body will be secreted in the bile and will render it bactericidal. The report by KAEWEL and KUHN (*Arch. f. exper. Path. u. Pharmakol.*, 1927, **125**, 242) gives some hope that such a substance may have been found. Experimenting on dogs with biliary fistula, they tested a number of different preparations of gold, silver, arsenic, mercury and others. The most effective of these was found to be a complex mercury compound of salizylallylamid-o-sodium acetate named salyrgan. It was used in 1 per cent solutions and could be recovered after intravenous injection in the bile which it made bactericidal to B. typhosus. In test-tube experiments, by adding B. typhosus to bile and varying amounts of salyrgan, it was found that the bile became sterile after twenty-four hours' incubation when the dilution of this substance was as high as 1 to 10,000. It has no apparent ill effects on animals in 1-cc. doses.

Spread of Diphtheria from Carriers.—In the reports of the study of dissociation of bacteria it has been suggested and at times definitely stated that the bacteria in carrier cases are not as virulent or pathogenic as they are in clinical cases. DOULL, STOKES and MCGINNES (*J. Prev. Med.*, 1928, **2**, 191) have studied epidemiologically the incidence of clinical diphtheria among family contacts of carriers of diphtheria bacilli and found the incidence measurably higher than in a control population. The incidence was, however, only about one-tenth that of those exposed to clinical cases. Even where the contact is with carriers of the so-called "avirulent" type, the incidence is higher than in the control persons. This increased incidence only lasts about one month and is followed by a period of two months with an attack rate below that of the control group. The explanation for this is given as possibly due to lessened exposure because the carriers have become immune, or to immunity acquired by the contacts or possibly to both factors.

Mobilization and Transfer of Clasmatocytes.—LINTON (*Arch. Path.*, 1928, **5**, 787) discusses mononuclear cells and immunity to streptococcic infections. He was led into this problem due to interest in reports by Gay, Linton and Clark on the relations of immunity between the two pleural cavities, where it was shown that immunization of one cavity against a streptococcic infection is coincident with immunization of the other cavity.

In rabbits with areas of granulation tissue in the peritoneal walls produced by intraperitoneal injections with aleuronat-starch mixture, intrapleural irritation with aleuronat and starch mixture results in the production of a subserous infiltration richer in clasmatocytes than in animals without such a peritoneal focus of cells. When from 150 to 250 times the minimum lethal dose of a highly virulent strain of hemolytic streptococcus is used intrapleurally in place of the aleuronat and starch mixture, the animals are found to be protected in 73 per cent of cases. The detailed study of the changes that occur under these circumstances in the pleural wall and pleural exudates, strongly suggests that participation of clasmatocytes from the peritoneum is the basis for the intrapleural immunity produced. Reinoculation of the cavities with multiples of the minimum lethal dose shows immunity in both pleural cavities for at least twenty days, and in the cavity previously inoculated for at least thirty days. The animals were also found immune to a further intrapleural inoculation given from forty to sixty days after the formation of the peritoneal focus.

HYGIENE AND PUBLIC HEALTH

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The Reaction in the Skin of the Normal Rabbit following Intradermal Injection of Material from Smallpox Lesions: the Specificity of this Reaction and its Application as a Diagnostic Test.—McKinnon and Defries (*Am. J. Hyg.*, 1928, **8**, 93) state that the intradermal injection of material from smallpox cases into normal rabbits evokes regularly a lesion having definite characteristics. The specificity of this reaction has been shown by the modified response of such inoculated rabbits to vaccine virus when applied to the skin. The intradermal injection of material from cases of chickenpox into normal rabbits fails to elicit such a reaction. Comparison of the lesions following the intradermal inoculation of test material into a normal rabbit, and, at the same time, into a vaccine-immunized rabbit, is advocated as a reliable procedure for the diagnosis of smallpox.

On the Specificity of Scarlet Fever Streptococci.—Zlatogoroff and Derkatch (*J. Infect. Dis.*, 1928, **42**, 56) state that streptococci derived from sources other than scarlet fever produce toxic substances (toxins). These substances cause a skin reaction of the Dick type under the same

conditions as the toxins of scarlatinal streptococci. Substances producing the phenomenon of extinction (Schultz-Charlton) may be obtained by immunization with scarlatinal as well as nonscarlatinal streptococci. A positive Dick reaction may be obtained during the period of scarlet fever complications with scarlatinal as well as nonscarlatinal streptococci. This fact brings us to suppose in this case a reaction to the unspecific bacterial proteins. Scarlatinal serums give the reaction of flocculation (precipitation) with toxins of streptococci derived from various pathogenic sources. Neither the toxin production nor the Schultz-Charlton test enable us to confirm the conception of the specificity of scarlet fever streptococci.

A Study of the Mechanism of Recovery from Experimental Pneumococcus Infection.—ROBERTSON, WOO, CHEER and KING (*J. Exper. Med.*, 1928, **47**, 317) made a study of the blood of cats and rabbits during experimental pneumococcus infection with a view to ascertaining the relationship of acquired immune properties to the mechanism of recovery. Observations were directed chiefly toward the detection of pneumococcidal promoting substances, but the other manifestations of antipneumococcus reaction were studied as well. It was found constantly that the serum of animals recovering from infection possessed the power to promote the destruction of highly virulent pneumococci in rabbit serum leukocyte mixtures which mixtures of themselves have no growth-inhibitory action. Furthermore, the presence of this serum immunity was associated with a marked increase in acquired resistance to the pneumococcus. In cats, which were studied in the most detail the pneumococcidal promoting power of the serum as well as the opsonic, agglutinative, and mouse-protective activities became demonstrable at the time of recovery and their appearance in the serum always marked the termination of blood invasion. These immune reactions were found to be type-specific. The animals which succumbed failed to develop detectable serum immune properties and showed persistent blood invasion. The degree of leukocytosis did not appear to bear any constant relation to the outcome of the disease. The significance of these findings is discussed.

A Comparison of the Spirochete of Yellow Fever (Leptospira Icteroides Noguchi) with the Leptospira of Weil's Disease.—The most noteworthy point which MARTINI (*J. Exper. Med.*, 1928, **47**, 255) observed in his studies was the extraordinary duration of life and the relatively meager requirements for sustenance of Leptospira icteroides. He states that it is conceivable that under natural conditions opportunities might arise for the prolonged existence of Leptospira icteroides, so that possibly after a lapse of years, the disease might reappear without introduction from outside. At any rate, the great viability of Leptospira icteroides must be considered in this connection. A decrease in the virulence of the leptospira does not rule out the possibility of a renewed outburst of yellow fever, since Uhlenhuth and Zuelzer have shown that it is possible to set up Weil's disease in guinea pigs by means of apparently saprophytic spirochetes obtained from drinking water, when the virulence of these organisms has been artificially heightened.

Studies in the Common Cold. II. A Study of Certain Gram-negative Filter-passing Anaërobes of the Upper Respiratory Tract.—A study of the Gram-negative, filter-passing, anaërobic organisms, described by Olitsky and Gates, and Gates and McCartney, was undertaken by MILLS, SHIBLEY and DOCHEZ (*J. Exper. Med.*, 1928, **47**, 193) with a view to determining the general character of the organisms and their possible rôle in the causation of the common cold. Three outstanding facts are apparent from the study: (1) The organisms in question from a heterogeneous group; (2) they are nearly always present in the upper respiratory tract, and (3) there is a decrease in their incidence during colds. The lack of homogeneity among the strains was striking. Variations in morphological and cultural characteristics were the rule, even in the subgroups, and very little serologic interrelationship was evident. The authors were unable to demonstrate either "cold" or "normal" strains. In regard to their heterogeneity these organisms resemble such poorly differentiated nonpathogens as B. coli or perhaps B. Pfeifferi. It is true that vriulent strains are sometimes noted among such organisms and it may be possible that such pathogenic strains exist among these Gram-negative filter-passing anaërobes, but no evidence was produced in support of this. The organisms seem to be part of the harmless normal flora of the upper respiratory tract. Probably their percentage incidence would rise higher than that noted in the present study (75 per cent), if cultural methods could be further improved. The reduction in their incidence in colds makes improbable the assumption that they bear a causal relationship to these infections. In fact, as pointed out above, this decrease is much more in keeping with the conclusion that they constitute part of the normal nonpathogenic flora of the upper respiratory tract, and would seem to bear no etiologic relationship to the common cold.

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